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PROCEEDINGS

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SCIENTIFIC PROCEEDINGS.

I (610)

Experimental pernicious anemia.

By **HERMAN M. ADLER.**

[From the Laboratory of the Danvers State Hospital.]

These experiments were performed on rabbits; fourteen rabbits in all were employed. Olive oil was fed in varying doses. Two feedings of 10 c.c. of olive oil per kilo of body weight sufficed to kill after 5 days. 6 c.c. per kilo weight killed in six days when fed daily. 5 c.c. per kilo weight did not kill but produced secondary anemia with blood crises presenting the picture of pernicious anemia—blood count 4 to 5,000,000, Hb. 50 per cent. or less, achromia, irregularity in size and shape, polychromatophilia, stippling, blasts.

Eight rabbits were thus subjected to chronic poisoning with olive oil. Of these, three had previously been daily fed (for about a year) 0.3 gram quinine. Three rabbits had been treated for three months with intravenous injection of 0.01 gram quinine daily. The remaining two received daily feedings of olive oil without previous treatment. In all of these rabbits the blood picture of secondary anemia developed within a few days. In four the blood picture of pernicious anemia developed in from 2–3 months. The anemia was not constant but varied considerably. The weight curve approximately followed the appearance of the blood; dropping sharply as the anemia became apparent, rising as the anemia improved. Five of these rabbits showed marked impairment of nutrition during the entire course, the younger ones being decidedly stunted in their development. The three rabbits that had been fed quinine per os showed less severe disturbances and none of them have thus far (after 1½ years) shown the picture of pernicious anemia. The weight and blood

conditions improved markedly when the feeding of oil was suspended.

Calcium lactate, lime water, Fowler's solution and tincture of ferric chloride were fed at different times with the olive oil without, however, appreciably diminishing the effect of the oil. The action of the olive oil depends upon its content of triolein (oleic acid). Pure oleic acid was fed to a rabbit and found to be no more toxic than olive oil.

A noteworthy phenomenon in the chronically poisoned rabbits was a swelling of the heels, evidently hematmata, which came on suddenly in all of the rabbits, furthermore a crusted suppurating skin lesion which appeared on the inner surfaces of the ears of six out of eight of the rabbits.

The post mortem examination of the rabbits which died after only a few doses showed practically nothing except a slight congestion of the small intestine. In the autopsies on rabbits which had received many doses general absence of fatty deposits together with fatty changes in liver, heart and kidneys and an atrophic condition of the spleen and lymphoid apparatus were noted.

From this and from the appearances observed in human beings suffering from pernicious anemia, it is fair to assume that the lymphoid tissue, particularly of the intestine, is chiefly concerned in handling the fat absorbed from the food by the intestine.

2 (611)

The influence of age on the symptoms following thyro-parathyroidectomy.

By **SUTHERLAND SIMPSON.**

[*From the Physiological Laboratory, Medical College, Cornell University, Ithaca, N. Y.*]

With regard to the question as to whether the thyroid and parathyroid glands become less and less essential to the organism as age advances there is some difference of opinion. Vincent and Jolly¹ found that in the various species of animals which they used (cats, dogs, foxes, monkeys, rats, guinea-pigs, rabbits), the symptoms following thyroidectomy and parathyroidectomy were

¹ Vincent and Jolly, *Jour. of Physiology*, 1904, xxxii, p. 80.

not influenced, to any extent, by age or sex. In the case of dogs the writer can corroborate this statement, but it appears to be otherwise in the sheep, as the following account of experiments on this animal will show.

In the course of another investigation² the thyroids were completely removed from eighteen lambs, from seven to eight months old, and twelve adult sheep, without, in the course of the six months which intervened between the operation and their slaughter, any apparent ill effects. There was no falling out of the wool, nor any of the other symptoms of myxœdema supposed to be associated with complete thyroidectomy, and several of the adults gave birth to full-time, and to all appearance, perfectly normal lambs.

From three of these lambs, at the age of two months, the thyroids were removed, the two external parathyroids being left behind, and from two others at the same age (also born of thyroidectomized mothers) all the thyroid and parathyroid tissue was taken away. The latter, in the course of ten and nineteen days respectively, developed typical and acute parathyroid tetany. In one, the first fit was fatal in less than an hour from the onset, the rectal temperature being 112° F. one minute after death, and in the other, which was killed during the fit, the thermometer reached 108.7° F. immediately before death.

The three from which the thyroids alone were removed developed into typical cretins.

In these three, about one year after the first operation, the two remaining external parathyroids were removed. As a result of this there followed what appeared to be some gastro-intestinal disturbance, and on three or four occasions, several weeks apart, each lasting about a week, some stiffness of the limbs, but nothing of the nature of acute tetany with rise of temperature, increased respiration, etc., which was so marked in the other two. These three sheep are still alive more than four months after the second operation.

In addition to the three above mentioned, other two adult sheep, aged two and seven years respectively, have had the com-

² Simpson and Hunter, *Quart. Jour. Exper. Physiol.*, 1911, iv, p. 340.

plete operation of thyro-parathyroidectomy performed on them and no noticeable symptoms have followed.

In the sheep therefore it would appear that both the thyroid and parathyroid glands are much more important organs in the young than in the adult animal, and consequently that they become functionally less active as age advances.

In relation to the influence of the parathyroids on calcium metabolism it is interesting to note that the two young lambs which showed acute parathyroid tetany were fed almost entirely on milk, rich in calcium salts, while the three which had the external parathyroids removed when they were about fourteen months old, and the other two parathyroidectomized adults, lived on a purely herbivorous diet in which potassium salts predominate. It may be, however, that in the young animal, where bone is being rapidly formed, the ratio between the demand for calcium and the supply is even greater than in the adult, although in the latter a far smaller quantity is being ingested.

In the case of the adult sheep the results of thyro-parathyroidectomy are in agreement with those of MacCallum¹ who from a similar operation found that "Practically no effect whatever was produced in these five sheep, although in at least three of them ample time elapsed for the development of symptoms." The other two died early of pneumonia, due probably to the administration of ether.

3 (612)

Peculiarity in the mode of entrance of the optic nerve into the eyeball in some rodents.

By J. A. BADERTSCHER.

[*From the Physiological Laboratory, Medical College, Cornell University, Ithaca, N. Y.*]

In the majority of animals the optic nerve enters the eyeball as a round compact bundle of nerve fibers and the optic disc is circular in outline or nearly so. While removing the eyes from the woodchuck and prairie dog for histological material, I observed that here there was an exception to the general rule in that the

¹ MacCallum, *Johns Hopkins Hosp. Bull.*, 1907, xviii, p. 335.

optic nerve became transformed into a band flattened antero-posteriorly before it entered the eyeball, and that the disc was linear instead of circular in outline. In these animals the disc consists of a long slender band, bending slightly dorsally in the center and gently widening at the ends. The absence of rods and cones along this band indicates that it is a true blind spot. As far as the investigation has been carried on, this form of optic disc was found to reach its greatest development in the prairie dog and has only been observed in members of the family *Sciuridæ*. Further investigation is necessary to show whether this peculiarity is limited to species of this family.

Johnson¹ has pointed out the presence of an elongated disc in the squirrel and marmot, but he makes no statement regarding the mode of entrance of the optic nerve into the *bulbus oculi*. As stated above, the optic nerve spreads out in an antero-posterior direction shortly after it enters the orbit and penetrates the coats of the eye in the region marked by the optic disc. In the woodchuck and prairie dog the flattened portion of the optic nerve is slightly concave on both the dorsal and ventral sides, and the latter is marked by a slight groove extending along the long axis of the nerve midway between the ends of the disc. The optic nerve from a short distance within the orbit to the chiasma has the usual cylindrical outline. This tendency of the nerve to bifurcate is also seen in the squirrel and chipmunk but it has not developed to the same extent as in the animals above mentioned.

In the rabbit's eye the optic nerve enters the eyeball as a cylindrical bundle of nerve fibers, from which one might expect the optic disc to be circular in outline, but this is not the case as has been observed by Johnson and figured by Haab.² The optic papilla is nearly circular but instead of the fibers radiating from it to the different parts of the retina they divide into two nearly equal portions which run in opposite directions toward the equator of the eyeball. From these two bands the fibers spread out to the different parts of the retina. The expansion of the optic nerve on the inside of the *bulbus oculi* of the rabbit, in contrast to its spreading out on the outside of the *bulbus* in some forms of the

¹ Johnson, *Phil. Trans. Roy. Soc.*, 1901, 194 B, p. 30.

² Haab, cited by Fuchs, "Physiologisches Praktikum für Mediziner," p. 227.

family Sciuridæ may suggest an intermediate stage in the process of evolution between the latter group and those higher mammals in which the fibers radiate to all parts of the retina from a circular optic disc. However, an extended investigation is necessary before any conclusion can be arrived at with regard to the possible taxonomic value of this character.

Experiments to trace the fibers of the optic tract are now in progress. As the optic nerve is spread out near the eyeball, it is a simple operation to cut either the inner or outer half for a study of the degeneration of its fibers.

So far I am not in a position to offer any opinion regarding the physiological significance of this peculiarity.

Note.—In the case of the squirrel and European marmot this peculiarity in the optic nerve is mentioned in Cuvier's "Leçons d'Anatomie Comparée," Tome 3B, p. 430.

4 (613)

Biological and toxicological studies upon *Penicillium puberulum* Bainier.

By **C. L. ALSBERG** and **O. F. BLACK.**

[From the Bureau of Plant Industry, Washington, D. C.]

This species when grown upon Raulin's solution, in pure culture, produces a new organic acid which has been termed penicillic acid. This acid gives a brownish-red solution when treated with a dilute solution of ferric-chloride. With ammonia it gives a deep red color. From the analyses, molecular weight determinations and other data, it seems probable that this acid belongs to the same general class of compounds as are found in lichens, and termed lichen acids. Like them, it is slightly bitter and irritating. Pharmacologically, it is moderately toxic, having an antiseptic action and being a protoplasmic poison. It is not astonishing to find substances of this class in fungi, since lichens are symbiotic forms, composed of fungi and algæ. The finding of this type of substances in the pure culture of a fungus makes it probable that in lichens, lichen acids are the product of the fungus metabolism, and not of that of the algæ.

5 (614)

The influence of the salts of calcium and potassium on the degree of hypertrophy produced by adrenalin injections in rabbits.

By **HUGH A. STEWART.**

[From the Department of Pathology, College of Physicians and Surgeons, Columbia University, New York.]

A series of experiments was conducted with a view to determine whether the antagonism between calcium and adrenalin, as recently described by Meltzer and Auer, Schrank and others, holds good also as regards the hypertrophy of the heart which adrenalin produces when injected intravenously into rabbits.

The method of investigation was as follows: One lot of rabbits was given every second day 0.2 c.c. of adrenalin chloride (1 in 1,000) in 2 c.c. of physiological salt solution. Throughout the whole series, twenty-four injections were given. A second lot received the same amount of adrenalin in 2 c.c. of a 10 per cent. solution of calcium chloride for the same length of time. Still a third lot was given 0.2 c.c. of adrenalin (1 in 1,000) in 2 c.c. of physiological salt solution every second day for twenty-four injections. The animals of this lot, however, were kept on a diet of carrots and potatoes only, the object being to give a diet containing a minimal amount of calcium. A fourth lot received the same amount of adrenalin in 2 c.c. of a 2 per cent. solution of potassium chloride.

As a result of these experiments, data were obtained which justified the following conclusions:

I. That calcium does not inhibit or prevent the hypertrophy of the heart produced by adrenalin.

II. That on a diet poor in calcium, the degree of hypertrophy is insignificant. From this it would seem that a certain percentage of calcium in the tissues is necessary in order that injections of adrenalin will produce hypertrophy.

III. The addition of potassium to adrenalin increases slightly the degree of hypertrophy.

6 (615)

Color inheritance in *Fundulus* hybrids.By **FRANK W. BANCROFT.**

[From the Rockefeller Institute for Medical Research.]

In the hybrids of *Fundulus heteroclitus* and *Fundulus majalis* it was found that, in general, wherever the color characters were not concerned with the rate of development, the *F. heteroclitus* characters were dominant over those of *F. majalis*. These dominant characters were:

1. Red yolk chromatophores large and abundant.
2. Black yolk chromatophores large and usually polygonal in shape.
3. An early first crop of head chromatophores is present, in addition to a later crop which is found in both pure species and both hybrids.
4. There is a row of red chromatophores on the lateral line shortly before and immediately after hatching. As soon as the fish hatch the red chromatophores begin to fade, and within a few days disappear entirely.

On the other hand, when the characters were concerned with the rate of development, the Mendelian dominance was partly or entirely obscured. These characters were:

5. In *F. heteroclitus* there are no or very few black chromatophores on the lateral line at hatching; but they increase rapidly during the first few days after hatching. In *F. majalis* there are 50 or 60 black lateral line chromatophores at hatching. The hybrids are intermediate.
6. In *F. heteroclitus* when the yolk chromatophores first appear they are uniformly distributed over the whole yolk; while in *F. majalis* they are confined to the hemisphere containing the embryo. The hybrids are intermediate.
7. Both with respect to time, and with respect to the stage of development of the embryo the yolk chromatophores appear first in *F. heteroclitus*, next in the *F. heteroclitus* egg hybrid, next in the *F. majalis* egg hybrid, and last in the pure *F. majalis*.

An apparent case of blended inheritance in the time of the

first appearance of head pigment was found to be really a case of the combination of two crops of head chromatophores, one of which did not develop in the recessive species *F. majalis*.

7 (616)

A note on the relation of the semi-circular canals of the ear to the motor system.

By **J. GORDON WILSON** and **F. H. PIKE**.

[*From the Laboratories of the University of Chicago and Northwestern University.*]

The work on the semi-circular canals was undertaken with the object of studying: (1) The results of stimulation of the end organ of the vestibular nerve; (2) the immediate and remote results of destruction of the labyrinth or of the eighth nerve on one or both sides; (3) the effect of removal of various parts of the brain on phenomena which have been observed to follow stimulation or destruction of the labyrinth, and (4) the paths of nervous connection between the labyrinth and the eye muscles — the optico-acoustic path. Later it is the intention to study anatomically the degenerative processes occurring in various parts of the central nervous system after destruction of the labyrinth or eighth nerve.

Method.—The mastoid bone is exposed by a skin incision and the separation of the muscles from their attachment at the linea nuchæ superioris and the anterior inferior border of the pars mastoidea. A trephine opening is made through the outer table and diploe of the mastoid bone. The hard portion of the otic bone, in which the semi-circular canals are imbedded, can be removed with a mastoid gouge and the labyrinth destroyed without direct anatomical injury to the cochlea. Dogs, cats and tortoises were used. The results here given apply to dogs, unless otherwise stated.

Results.—Immediately following recovery from the anesthetic after removal of one labyrinth, there is marked torsion, particularly of the anterior part of the body, of the animal toward the injured side. The animal is unable to walk and falls over toward

the injured side on attempting to stand. It may roll completely over on the floor. There is a quick movement of the eyes toward the sound side and a slow return to the injured side. The unsteadiness of gait and the nystagmus are transient. Marked torsion of the head is permanent (two years).

Stimulation of the labyrinth, under moderate anesthesia, by putting hot water in the trephine opening before destruction of the semi-circular canals, causes slow marked deviation of both eyes to the opposite (unstimulated) side. Ice in the trephine hole causes the eyes to deviate to the same (stimulated) side. On electrical stimulation, the zinc terminal of a battery causes deviation to the opposite side; the carbon terminal, to the same side.

The deviation of the eyes on stimulation of the labyrinth may be obtained after total removal of the cerebrum, the optic thalamus, the anterior portion of the anterior corpora quadrigemina and the cerebellum. The torsion of the head in tortoises following destruction of one labyrinth is as marked after decerebration as before. There are no apparent "shock" phenomena in these reflexes after decerebration.

The nystagmus is not due to irritation of the wound, but to the action of the opposite uninjured labyrinth. Nystagmus following extirpation of the second labyrinth is much less marked, and more fleeting than after extirpation of the first, and is reversed in direction, *i. e.*, the quick movement is to the injured side.

There is no torsion of the body nor any rolling movements after extirpation of both labyrinths at the same operation, nor when the second labyrinth is destroyed after an interval. The animal becomes very ataxic and is unable to grasp food if both labyrinths are removed at the same time.

Complete or partial removal of the cerebellum one or two weeks previous to removal of one labyrinth has no effect upon the onset and course of labyrinthine nystagmus. Eye movements following injury to the cerebellum are jerky, irregular, and quick in all directions. Labyrinthine nystagmus is slow in one direction and quick in the opposite direction. The eye movements following cerebellar extirpation greatly outlast those of labyrinthine origin, and the labyrinthine movements may be superposed on those following cerebellar removal.

Removal of one or both occipital lobes of the cerebrum does not abolish labyrinthine nystagmus. True labyrinthine nystagmus has never been observed after complete decerebration, although the slow deviation of the eye persists. The slow component of nystagmus is of labyrinthine origin. The quick component is probably of cerebral origin.

The results suggest that the vestibular mechanism is connected far more closely with the phylogenetically older motor system (von Monakow) than with the phylogenetically newer system.

8 (617)

Experimental nephritis in guinea-pigs by subcutaneous injections of chromates.

By **W. OPHÜLS.**

[From the Pathological Laboratory of Cooper Medical College and Stanford University.]

After having determined that 1 centigram of bichromate of potash is very nearly a lethal dose for guinea pigs of from 500–750 gm., forty guinea pigs were used in an effort to produce, if possible, lasting anatomic lesions in the kidneys by repeated injections. Great difficulty was encountered in continuing larger doses on account of the extensive necroses produced at the site of injection. In the end it was found that a $\frac{1}{2}$ – $\frac{1}{5}$ per cent. solution of chromate of potash to which an equal amount of carbonate of soda had been added was most satisfactory, although still quite irritating. As our experience has taught us that sublethal doses are most effective in experiments of this character, injections of one or one half centigram were used in one half of the experiments and the doses crowded as closely as the animals would tolerate; in other series smaller doses down to a quarter of a milligram were employed and continued for long periods (in one case for nearly two years). The immediate effect of the injection of large doses in the guinea pig is the production of an albuminuria which is usually quite limited in amount and the appearance in the sediment of desquamated cells from the uriniferous tubules, much more rarely of casts. The kidneys in the acute intoxication

are very markedly hyperemic, there is more or less fatty degeneration and well marked necrosis and desquamation of the epithelium, later cast formation also occurs. The glomeruli are hyperemic, do not show any distinct histologic lesions. Hemorrhages from them were not observed. The lesions are hardly severe enough to account for the early death of the animals. I have become rather strongly persuaded that the chromates cause death in guinea pigs not primarily by their action upon the kidneys, but in a different way, although nothing definite could be ascertained in this regard.

Results with Injections of One Half Centigram.—Several guinea pigs died from the first or second dose. Four lived from five months to 15½ months. The immediate reaction from each dose was well marked and it was impossible to give the doses very frequently; the highest was 12 doses in five months. One of these animals receiving five doses in seven months showed merely cystic dilation of some glomeruli similar to that which was observed in controls;¹ in one, apart from well marked epithelial lesions, there was a slight diffuse interstitial process; the other two showed definite small areas of collapse of degenerated tubules but with very little evidence of new formation of connective tissue between them.

Results with Injections of One Quarter of a Centigram.—Few animals died after the first injections; the immediate reaction on the part of the kidneys in most instances was very slight and the doses could be repeated more frequently. Some of these animals lived for one year or more, one for nearly two years. All showed more or less well marked epithelial lesions with formation of casts, very few interstitial lesions of a character which was not encountered in the controls also. In these few there were small areas of collapse of degenerated tubules and very little new formed connective tissue between them.

Experiments with smaller doses even when very frequently repeated and continued for long periods were entirely negative so far as the kidneys were concerned.

Hearts and bloodvessels remained normal in all animals.

The conclusion seems justified that it is impossible to produce

¹ See Ophüls, "Occurrence of spontaneous lesions in kidneys and livers of rabbits and guinea pigs," *Proc. Soc. for Exp. Biol. and Medicine*, 1911, viii, 75.

severe lasting renal lesions in guinea pigs with chromates, probably because in these animals the chromates are too toxic in a general way and too slightly effective on the kidneys locally.

9 (618)

Experimental nephritis in rabbits by subcutaneous injections of chromates.

By **W. OPHÜLS.**

[From the Pathological Laboratory of Cooper Medical College and Stanford University.]

Rabbits are relatively more susceptible to the action of chromates than guinea pigs. Animals of from 2,000–2,500 gm. in weight sometimes die after the injection of two centigrams of bichromate of potash. The acute renal lesions produced by large sublethal doses are much more marked than those found in guinea pigs under similar conditions. There is marked albuminuria, much degeneration, necrosis and desquamation of the epithelium and abundant formation of casts of different kinds. The extreme lesions which may develop after a while as a result of crowding of large doses were described by me in 1908,¹ but they do not necessarily follow even repeated administration of large doses.

Fifty animals were experimented upon. The dosage varied between two centigrams and two milligrams. Some of the animals were kept alive for a year or more. So far as epithelial lesions are concerned the experiences are similar to those in guinea pigs, except that the epithelial lesions became more severe and seemed to continue longer after the last injection. Very marked interstitial lesions were observed at times, but they resemble those observed spontaneously² so closely and occurred so irregularly, sometimes soon, sometimes late after the administration of various doses and sometimes not at all, that any definite conclusion of their relation to the injections could not be arrived at.

Hearts and bloodvessels remained normal in all animals.

¹ Ophüls, "Some interesting points in regard to experimental chronic nephritis," *Journ. Med. Res.*, 1908, xviii, 49.

² Ophüls, *l. c.*

10 (619)

A dominant sex-limited character.By **T. H. MORGAN.**

[From the Department of Zoölogy, Columbia University.]

A new mutant of the fruit fly, *Drosophila*, characterized by abnormal arrangement of the black bands on the abdomen, proves to be dominant to the normal arrangement of the bands, and since the factor for the character is coupled with femaleness it may be assumed to be contained in the X-chromosome. Abnormal ♀ by normal ♂ gives abnormal males and females. These inbred produce in the next, or F₂, generation 50 per cent. abnormal ♀, 25 per cent. abnormal ♂ and 25 per cent. normal ♂. No normal females appear in this generation. Thus the *normal character* is sex-limited in relation to the abnormal.

The reciprocal cross, viz., normal ♀ by abnormal ♂ gives abnormal females and normal males. These inbred produce in the next, or F₂, generation, 25 per cent. abnormal ♀, 25 per cent. normal ♀, 25 per cent. normal ♂, and 25 per cent. abnormal ♂¹. The explanation is as follows:

Abnormal ♀ = Ab. X — Ab. X.	
Normal ♂ = N. X ———.	
F ₁	♀ Ab. X N. X.
	♂ Ab. X —
F ₂	Ab. X Ab. X = Ab. ♀.
	Ab. X N. X = Ab. ♀.
	Ab. X = Ab. ♂.
	N. X = N. ♂.

It will be seen that the abnormal factor is contained in X, hence sex-limited inheritance. The explanation of the reciprocal cross will be clear from this example.

Five other cases of sex-limited inheritance have been found in *Drosophila*, viz., miniature wings, rudimentary wings, black color, bright red eye and orange eye. All of these are recessive characters, and *ex hypothesi* are also present or absent from X. By crossing a red-eyed, abnormal type with a white-eyed, normal

¹ Since the abnormal character overlaps the normal some difficulty is found in classifying the F₂ generation.

type two points are established: first, that the same chromosome *X* may carry both a recessive (absence) and a dominant character at the same time, and second, that a strong "association" or coupling of characters exists. Thus, when an abnormal red-eyed ♀ is paired with a normal white-eyed male the offspring are abnormal red-eyed males and females. These inbred have given in the second generation:

Abnormal red	♀		18
Abnormal red	♂		6
Abnormal white	♂		0
Normal red	♀		18
Normal red	♂		6
Normal white	♂		14

A strong tendency for the grandparental combination to reappear in the F_2 generation is manifest.

The reciprocal cross, viz., abnormal red-eyed ♂ by normal white-eyed ♀ gives abnormal red-eyed females and normal white-eyed males. These inbred have produced:

Normal white	♀		47
Normal white	♂		55
Abnormal white	♀		0
Abnormal white	♂		4
Normal red	♀		34
Normal red	♂		19
Abnormal red	♀		41
Abnormal red	♂		48

Here also the normal and white combination reappear, while the abnormal and white are scarcely represented.

Trypanosomiasis in monkeys (*Macacus rhesus*) in captivity.By **B. T. TERRY.***[From the Laboratories of the Rockefeller Institute for Medical Research, New York City.]*

In the blood of an experimental monkey (*Macacus rhesus*), Dr. Richard Lamar found on October 28, 1911, an actively motile trypanosome. This discovery led to my examining the blood of all of the monkeys at the Rockefeller Institute.

In examining 130 monkeys, 28 were found infected with trypanosomes. The infected monkeys had been used for experiments between July 17 and October 6. Six monkeys used on or before July 17 were negative, and 80 others, some normal, the rest used after October 6, were also negative.

With but one exception, all of the monkeys examined belonged to the *Macacus rhesus* species.

The trypanosomes found in the 28 monkeys were apparently of the same kind. They have been successfully inoculated into one monkey (*Macacus rhesus*), six mice, two rats, one guinea pig, and one young rabbit. In none of these animals has a rich infection been seen. The two rats were infected on the 8th day, the six mice between the 9th and the 52d day, the guinea pig and rabbit on the 16th day, and the monkey between the 16th and the 24th day. The trypanosomes do not appear to be very pathogenic.

The micronucleus is usually at the extreme posterior end of the parasite, is strikingly large, measures 1μ or more in diameter, and often projects on either side of the parasite. The nucleus is oval, measures $1\frac{2}{3}$ to $2\frac{2}{3}\mu$ in its long diameter, and is situated near the juncture of the anterior $\frac{1}{3}$ and the posterior $\frac{2}{3}$ of the body. The flagellum is very long, the free part measuring 10 to $12\frac{1}{3}\mu$. The entire length of the parasites thus far measured has varied between 25 and 28μ , the breadth between 2 and $2\frac{1}{4}\mu$.

If the future shows that the trypanosomes here described

belong to a new species, I propose for them the name *Trypanosoma rhesii*.

2 (621)

**On the question of immunization against transplantable cancer
by injection of an animal's own tissues.**

By **R. A. LAMBERT.**

[From the Department of Pathology, College of Physicians and Surgeons, Columbia University.]

That the injection of a suitable quantity of homologous tissue induces in susceptible mice a certain degree of resistance to the inoculation of their transplantable cancers is a well-established fact. There appeared recently a paper by Woglom¹ in which experiments were described showing that autogenous tissue (spleen) injected subcutaneously was also capable of inducing this immunity. Woglom's work has been questioned by Apolant² who repeated the experiments with negative results. Apolant maintains further that the spleen of a mouse does not afford sufficient tissue for immunization, and that the question as to the possibility of immunizing with an animal's own tissues is still an open one.

In the experiments herewith reported, blood has been used as the immunizing agent. The quantity of defibrinated blood necessary for immunizing young mice was shown by Bashford to be about .3 c.c. In order to eliminate, however, the possibility of insufficient dosage, it was considered desirable to use at least .5 c.c. As Woglom stated in his paper, mice cannot be bled this amount plus the loss attending the bleeding without causing death. Interval bleedings from the jugulars were therefore resorted to. In nearly all of the experiments two bleedings only, on successive days, were necessary. About ten drops of blood in citrate solution were taken each time. The corpuscles were preserved in the ice box and injected subcutaneously on the day after the last bleeding. Ten mice were treated in this way; ten controls were injected with a similar quantity of homologous blood; ten normal mice were set aside as controls on the two

¹ *Jour. Exp. Med.*, January, 1910, p. 29.

² *Zeit. f. Immunitätsforschung*, July, 1911.

treated groups. The mice were all young and thrifty; average weight, 18 grams. The three series were inoculated with carcinoma ten days later. The record of the tumors resulting from these inoculations shows a definite immunity in the series treated with homologous blood, but practically no difference between the normal controls and those receiving injections of their own blood.

These findings, then, indicate that immunity against transplantable cancer in mice is, at least, not regularly induced by injections of an animal's own tissues. A larger series would probably be necessary to determine the existence of individual variations in the reaction of animals to such injections.¹

3 (622)

Another case of sex-limited heredity in poultry.

By **C. B. DAVENPORT.**

[From the Carnegie Institution of Washington.]

To the four or five described cases of sex-limited heredity in poultry another is added.

The Jungle-fowl and its derivative, the Brown Leghorn, have the hackle and saddle feathered "laced" with red. The upper wing coverts of the cock are also red, forming the "wing bar." In the Dark Brahma, on the other hand, the red is not formed on the hackle and saddle and is nearly absent on the wing bar of the male, so that the red is replaced by white.

If, now, a male Dark Brahma be crossed with a female Brown Leghorn, or if the cross be made in the opposite direction, all sons are white-laced; but the wing bar is red. Thus, in these sons the white lacing is dominant but the white wing bar appears to be recessive. The most important point, however, is that the sons derived from the reciprocal crosses are practically indistinguishable.

With the daughters this is by no means the case. When the father is white-laced, the daughter is also; but if the father is red-

¹ A second set of experiments has been done which shows a slightly larger percentage of resistant animals among those immunized with autogenous tissue than among the normal controls. The difference, however, is not sufficiently striking to influence the conclusion drawn from the first experiments.

laced the daughter is likewise; *i. e.*, the daughter's lacing comes from the father's side of the house only.

The explanation is simple on the assumption that the lacing is linked with the sex-chromosome, following the scheme of transmission of the sex-chromosome as worked out by Stevens, Wilson and Morgan. While the male of poultry must have two somatic sex-chromosomes the female has only one. Therefore, while all sperm possess a sex-chromosome, only half of the eggs do. In the fertilized egg or zygote that has only one sex-chromosome, this is derived from the father and the zygote becomes a daughter. Hence the daughter "inherits" from the father only.

The hybrids have been bred together and a second generation has been obtained. When the hybrid male is mated to a white-laced hybrid female all the sons are white-laced while half the daughters are white-laced and half red-laced. But when the hybrid male is mated to a red-laced female half of the sons are white-laced and half red-laced while half of the daughters are white-laced and half red-laced as in the reciprocal mating. This result accords with the hypothesis.

4 (623)

The gastric and pancreatic secretions of the newborn.

By **ALFRED F. HESS.**

[From the Department of Health, New York City.]

I have been able by means of a simple duodenal catheter to obtain for the first time access to the duodenum in the living infant. This has enabled me to investigate the secretion of the upper part of the small intestine. This catheter is, in brief, merely a Nelaton soft rubber catheter No. 14 (F). That I actually do reach the intestine is proved by X ray photographs which I show.

The present report concerns solely newborn infants, which had never obtained any nourishment. I have found some interesting conditions not only as concerns intestinal secretions but also regarding the secretion of the gastric juice. It is noteworthy that there have been no previous investigations in this regard; in fact I have been able to find note of only one test of the gastric secretion of the newborn before it has been given food.

I found that in almost all cases hydrochloric acid is present in the stomach of these newborn infants whether they are examined one half hour or twenty hours after birth. The hydrochloric acid varies from $\frac{1}{2}$ cu. cm. to about 7 cu. cm., and is not in direct proportion to the age of the child. This hydrochloric acid is not stimulated merely by the passage of the tube, for it was obtained within a minute or two after the catheter was introduced. It, therefore, must have another origin. I believe that it is a reflex due to the sucking of the tube. The longer the catheter is kept in the stomach the more juice is obtained; in one hour 14 cu. cm. was obtained; in an hour and 50 minutes 17 cu. cm. This gastric juice has an acidity on an average of about 50. Pepsin and rennet were also present in considerable amount.

These facts show that the infant at birth is prepared to digest food. The large amount of hydrochloric acid may be present in order to digest the high percentage of proteid of the colostrum and it may also serve the purpose of a bactericide, for we have found it to possess high bactericidal power.

The duodenum also was entered by means of the catheter. It can be entered almost as easily and quickly as the stomach in the newborn infant, and the contents aspirated. It was found that in the newborn infant there is very little to be aspirated from the duodenum compared to older infants. In spite of the fact that a large amount of hydrochloric acid is present, this does not seem to stimulate to a proportional degree the flow of the duodenal secretion. However, I have been able by this method to find protease, lipase, and amylase in the duodenum before any food was ingested, and, therefore, can state that the hydrochloric acid is sufficient hormone to stimulate these ferments. Amylase was found with least regularity. Frequently no secretion at all was obtained. In all about 35 tests were undertaken.

It is of special interest to note that bile was not found in these tests. It was expected that this would be quite otherwise, as the meconium is rich in bile, and we know that bile is found in the gall bladder of the fetus by the fourth month. I have not tested for the presence of the bile salts. Many other problems suggest themselves for investigation by this method; with some of these I am at present occupied.

5 (624)

Nitrogen and sodium chloride excretion in experimental uranium nephritis.¹By **HERMAN O. MOSENTHAL.**

*[From the Departments of Biological Chemistry and Medicine,
College of Physicians and Surgeons, Columbia University,
New York.]*

A series of experiments were performed upon dogs with the object of determining the effects on the output of nitrogen and sodium chloride in nephritis produced by the subcutaneous injection of uranium nitrate. These dogs were fed the usual standard diets, also diets containing much meat, as well as food to which considerable amounts of urea and sodium chloride had been added.

The results of these experiments appear to justify the following conclusions regarding uranium nephritis.

1. The nitrogen secreted by the small intestine, as determined by the Thiry fistula method, is somewhat diminished.
2. The fecal nitrogen remains approximately unchanged.
3. The urinary nitrogen is not diminished even when the diet demands an excretion of one gram of urinary nitrogen per kilo of body weight of the dog.
4. In some cases the urinary nitrogen is increased. The source of this excess of nitrogen is problematical. It may be due to protein destruction of the body tissues caused by the same toxic agent as the nephritis. If this be true, the "rest" nitrogen of the blood serum should be higher than normal. Experimental attempts have been made to ascertain the facts in this connection but have not been pushed far enough to warrant a definite statement.
5. The sodium chloride excretion in the urine keeps pace with the intake even when considerable quantities are added to the food.
6. The above statements have held true for dogs after the first as well as after several large single injections of the drug at long intervals. One animal was tested after he had received as many as seven injections.

¹ Under the auspices of the Edward N. Gibbs Memorial Prize Fund.

The seat of action in tetany after parathyroidectomy.By **W. G. MACCALLUM.**

[From the Department of Pathology of the College of Physicians and Surgeons, Columbia University.]

Both the immediate cause and seat of tetany are still obscure. It has been suggested, though never proven, that a poison must circulate in the blood to cause the tetanic twitchings. It has also been suggested that these twitchings may result from a lack of calcium in the circulating fluids. It has been shown that tetany does not appear in a limb to which the nerves have been cut. It is conceivable that this is due to the fact that no impulses reach that limb from the spinal cord. The present experiments show that if the nerves be cut during tetany, their electrical excitability remains the same as that of the intact nerves on the opposite side. Further, it is shown that if the nerves be cut before the development of tetany, they become hyperexcitable to an extent which equals that of the intact nerve on the opposite side, although they are quite separate from the spinal cord. Since degeneration occurs within two or three days, such observations must be made with due regard to this fact. The peculiar character of this rise in the excitability is seen in the figures obtained for the cathode and anode opening shocks to which the nerves become especially excitable. In complete anemia or after the death of the animal there is a period of about one half hour during which this characteristic rise in the excitability of the nerve to the cathode and anode opening shocks appears. Nevertheless, the excitability of the nerves is, throughout this period, very much lowered and the curve is in no way comparable, therefore, to that in tetany.

Transfusion of the blood of an animal in tetany into the vessels of a normal animal has not succeeded in producing a characteristic tetany nor even a marked change in the excitability of the nerve.

This is probably partly due to inadequate technique and partly to the action of the normal dog's parathyroids. If the leg of a normal dog be isolated, with the exception of the nerves which

remain in intact connection with the spinal cord, and if the vessels be anastomosed with those of a dog in tetany, so that the peripheral portions of the normal leg are bathed with tetany blood, the nerves of that leg assume the characteristic hyperexcitability of tetany, and twitchings may even occur. Reestablishment of the connection with the normal circulation brings back the excitability to normal.

From these experiments, it may be concluded that the hyperexcitability is peripheral and is dependent upon some change in the character of the blood. Experiments with curare, to determine whether or not this is an affection of the nerves alone, have not yet been completed, although one has the general impression that the excitability of the muscles themselves is increased over normal. The value of the experiments is thought to lie particularly in the opportunity which is offered for the study of tetany blood modified in various ways and used as the fluid for perfusing an isolated extremity.

7 (626)

Curves from a case of transient complete heart block, showing constantly varying ventricular complexes.

By **ALFRED E. COHN.**

*[From the First Medical Division, Mount Sinai Hospital,
New York.]*

The patient from whom the curves were taken has been under observation since August, 1910. He was at that time suffering from cardiac decompensation. It was clear from the physical examination that he had a valvular defect. Combined arterial and venous curves were made. These showed that for short periods every impulse from the auricles was answered by a ventricular contraction, while at others the ventricular contractions responded to every second beat of the auricles. Curves were taken in February and March, 1911. These were volume curves from the jugular vein and radial artery and likewise curves of the cardiac action current, registered with an Edelmann string-galvanometer. At first the ventricles responded to every second

auricular beat, but somewhat later there was complete dissociation between the two pairs of cavities. Before the patient left the hospital, the relation between the auricles and ventricles was normal. Electric curves were taken on December 19, 1911, when the ventricles responded to every auricular contraction.

The curves which are of interest date from the period of complete auriculo-ventricular dissociation. Each ventricular complex is represented by *R*-, *S*-, and *T*-waves. They vary from each other in that, when the *R*- is large, the *S*-wave is small; and that when the *S*-wave is large, the *R*-wave is small. The *R*-wave gradually increases in size and then gradually diminishes, when the *S*-wave gradually increases in size and as gradually diminishes. If the apexes of succeeding *R*- and *S*-waves, *i. e.*, the significant wave in each complex were joined, a waved line would result. So diagrammatic a sequence as this did not occur frequently, but there was a tendency to approximate to this description. Sometimes the transition from complexes of one type to those of another was abrupt. The time between the complexes was almost equal, except at points of transition, when it was reduced.

It is concluded from the variation in the shape of the complexes, that they are responses to stimuli arising at levels in the heart varying from some supraventricular position to the apex. The explanation of the shortened time at points of transition is difficult. No hypothesis yet suggested is satisfactory. The fact that there was merely a temporary and not a permanent dissociation may be a significant factor, although the *P*-*R* interval associated with the transitions is not of uniform length. (*P* is the wave representing auricular systole.)

8 (627)

Further observations on the tolerance of gases by the circulatory apparatus.

By **J. P. ATKINSON** and **C. B. FITZPATRICK.**

[*From the Department of Health, City of New York.*]

In the *New York Medical Journal* of November 26 and at the New Haven meeting of December, 1910, we gave observations on the quantities of gas (air) tolerated and the apparent relation of

the adrenals to this tolerance. We have further determined that section of the cord between the fifth and sixth cervical vertebrae interferes with this tolerance of gas (air). After the removal of the adrenals from two dogs *carbon dioxide* was tolerated up to 942 c.c. in one case and 952 c.c. in the other, in 1 hour and 23 minutes.

Two dogs were injected with *nitrogen*.¹ One received 32 c.c. in six minutes with marked depressions; the animal lived. Panting occurred. The other received 272 c.c. within 22 minutes and died; panting was not noticed. The lungs were collapsed at autopsy.

The tolerance of *oxygen* was tested on two dogs. One received 150 c.c. slowly and survived. The other received 312 c.c. in 23½ minutes and died. During the oxygen experiments, panting occurred. The lungs were practically normal.

The tolerance of *hydrogen* was tested in two dogs. In one 184 c.c. in 8 c.c. volumes were injected in 13½ minutes. Each injection caused a moderate depression. 60 c.c. were given in 20 c.c. volumes in 3½ minutes, and 20 c.c. in 5 c.c. volumes. The large volumes caused great depression and almost death. In the other dog 90 c.c. were injected in 7 minutes in 8 c.c. volumes without harmful results.

Sulphuretted hydrogen was used to study elimination on two dogs. Three c.c. saturated H₂S water were injected into the femoral vein. The breath almost immediately blackened lead acetate. Twenty-five minutes after tying and clamping off the adrenals 3 c.c. more of saturated H₂S water was injected and a similar result was obtained. 100 c.c. of H₂S water introduced into the rectum did not give the reaction at the mouth in 25 minutes. In the other dog 30 c.c. of H₂S water were injected into the duodenum. In 8 minutes it was detected at the mouth.

¹ In every case morphin sulphate was given before etherization of the dog. Each dog was killed and autopsied after the experiment.

9 (628)

The destruction of adrenalin by spinal fluid.By **S. J. MELTZER.**

[*From the Department of Physiology and Pharmacology of the Rockefeller Institute.*]

Soon after the discovery of the profound effect of adrenal extract upon blood-pressure the question arose as to the fate of this extract in the blood. The rise of the blood-pressure after an intravenous injection of adrenin passes off in a few minutes and none of the adrenin is found to persist in the blood, no matter how large the injected dose has been. The quite natural explanation of this phenomenon was, that the blood destroys adrenin. But Oliver and Schäfer found that in a mixture of adrenin and blood, even after standing for 22 hours, the adrenin remained unaffected. It has been confirmed since by several investigators, that neither blood nor serum is capable of destroying adrenal extract. I shall not discuss for the present the problem of the fate of adrenin in the body in general. I wish only to report the discovery of the fact that there is at least one body fluid which is capable of destroying adrenin and that is spinal fluid. The observation was made by mixing human spinal fluid with adrenalin. The spinal fluids were obtained in the first place from a number of cases of poliomyelitis of the Rockefeller Hospital and from two cases of tuberculous meningitis, obtained for me by Dr. Flexner. But this destructive action is not specific to these diseases. I found it to be possessed by spinal fluids from cases of resolving pneumonia, gastro-enteritis and eczema, obtained through the kindness of Dr. Wollstein. Evidently it is a physiologic property of normal spinal fluids, although there seems to be a difference in degree of action between some pathologic cases; for instance the spinal fluid from poliomyelitis seems to destroy adrenalin definitely more readily than that from tuberculous meningitis. *This fact might attain a practical significance.* The presence of adrenalin was studied by its dilating action upon the frog's pupil (the so-called Meltzer-Ehrmann reaction) and its action upon blood-pressure.

The tracings speak for themselves. The mixture of adrenalin with spinal fluid in proportion of 1:20 when kept on ice caused a considerable rise of blood-pressure by a dose of 0.5 c.c., while when this mixture was incubated for an hour in the thermostat at 37° C. even 4 times the dose caused no change in blood-pressure.

10 (629)

Glucuronic acid determination (Tollens) in duodenal obstruction.¹

By **JOHN WILLIAM DRAPER AND FREDERICK W. SCHLUTZ.**

While the liver generally plays a subordinate part in the synthesis of glucuronic acid, it would seem from the experiments of Pohl (1), that upon the incorporation of chloral-hydrate or camphor, the conjugation of these substances with glucuronic acid does take place largely in that organ.

We have been interested in seeking a measure of the functional activity of the liver before and after experimental duodenal obstruction. By giving a dog camphor and determining the output of camphor-glucuronic acid, both before and after obstruction, we hoped to measure at least in a relative way any impairment in liver function which may follow this intestinal lesion.

The experiments were carried out on dogs—the operative portion under complete ether anesthesia. The animals were fed for fully a week on an exclusive meat diet in order to free the urine as much as possible from pentoses.

For the glucuronic acid determinations we employed one of the two methods described by C. Tollens (2, 3), viz., distillation of the glucuronic acid lacton with dilute hydrochloric acid, and precipitation of the resulting furfural with phlorglucin. This method seems open to less objection than most of the other quantitative methods which have been proposed. In the hope of further determining the accuracy of our results, we are now experimenting with the CO₂ method described by Tollens.

¹ Studies from the Laboratory of the Department of Physiology, University of Minnesota, Minneapolis, and from the Laboratory of Surgical Chemistry and Physiology, Rochester, Minnesota.

The experiments here reported were carried out as follows: The glucuronic acid excreted during one or two 24-hour periods was determined and used as a normal. According to Tollens, the variations in the daily quantities of glucuronic acid are very slight, if the diet is uniform.

From 2 to 5 gm. of commercial camphor dissolved in olive oil were given subcutaneously and the camphor-glucuronic acid excretion in the urine determined for three to four 24-hour periods. The duodenum was then obstructed by cross section and infolding at a point just aboral to the greater pancreatic duct. From 12 to 24 hours after obstruction, determined by the first indication of marked clinical symptoms, the same dose of camphor was again given and the camphor-glucuronic output determined in 24-hour periods until death ensued.

Including a report made by Draper (4) on one dog, we have completed experiments on three dogs. The results, expressed in per cent. of recovered camphor-glucuronic acid, are as follows: From Dog No 30, before obstruction, 41.76 per cent. of a theoretical total was recovered. From Dog No. 124, 44.00 per cent., and from Dog No. 128, 43.47 per cent. After obstruction, from Dog No. 30 was recovered 27.19 per cent. of a theoretical total; from Dog No. 124, 19.29 per cent. and from Dog No. 128, 18.05 per cent. Somewhat less than one half the camphor given during the normal period was recovered in the urine as camphor-glucuronic acid. What becomes of the balance is a matter of conjecture. The results obtained by Schlutz (5) in an earlier study differ from the above but this can probably be accounted for by the inferiority and uncertainty of the polarimetric method. This was at the time considered the method of choice.

The histological examination of the livers, hearts, spleens and kidneys of the animals cited in this report was negative except for a moderate capillary dilatation in a few of the sections. The nitrogen metabolism remained unchanged in Nos. 30 and 124. It was not determined in No. 128.

The above results from their uniformity suggest accuracy for the method so far as it goes and the marked decrease after operation implies possible diminution of certain liver functions after duodenal obstruction.

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II (630)

**The convulsant effect of the removal of the heart upon frogs
which had injections of morphin. A demonstration.**

By **T. S. GITHENS** and **S. J. MELTZER.**

*[From the Department of Physiology and Pharmacology of the
Rockefeller Institute.]*

Last April it was reported from this laboratory that (1) substances which are capable of causing a definite biological reaction in frogs cause the characteristic reaction also when injected after the removal of the heart, and (2) that some substances, like morphin and acid fuchsin, appear to be even more effective in cardiectomized than in normal frogs. The first phenomenon was explained by the theory that distribution in frogs deprived of the cardio-vascular circulation is accomplished by a peripheral mechanism, namely, by the tissue spaces, which present a connected system throughout the body. The second phenomenon was interpreted by the hypothesis that the fresh blood in the cardio-vascular mechanism continually antagonizes the convulsant action of such substances as morphin and acid fuchsin. The study of the last mentioned hypothesis and the underlying phenomenon has been hampered by the fact that the distribution by the peripheral mechanism is necessarily a slow one and since, at the warmer seasons, frogs survive cardiectomy only a short time, it happens that the animals die before the convulsant effect could make its appearance. We have therefore tried to study the hypothesis by the reversed method, that is, morphin injected first and the heart removed later. This was carried out in several series, the doses varying from 0.1 to 0.5 mg. of morphin per gram frog, and the intervals between the injection and the subsequent removal of the heart varying from a few minutes to 4 hours. We shall not enter

upon details: we shall merely state that the result was strikingly positive. While the morphin frogs, which were kept with hearts intact, remained normal, all the frogs which received proper doses of morphin and had their hearts removed at different intervals, developed tetanic convulsions, which in many cases had to be characterized as very violent. With doses of 0.25 mg. per gram frog, convulsions developed in practically every case, no matter how soon or how late the heart was removed. After intervals of 60 minutes and longer the result was positive practically with every dose between 0.2 and 0.5 mg. per gram frog. (The essential points were demonstrated before the Society.)

12 (631)

Intravascular foreign bodies.

By **C. C. GUTHRIE** and **A. H. RYAN.**

*[From the Laboratory of Physiology and Pharmacology,
University of Pittsburgh.]*

Experiments were performed by introducing sterilized (1) untreated, (2) oiled silk, and (3) human hair into arteries and veins and observing the results. Twelve common carotid arteries and twelve external jugular veins were employed. The number of silk strands varied from the smallest single strands used in blood vessel suture to twenty-four such strands. Where a number were used they were threaded into suitably large needles and were not twisted. Cambric needles were used.

The experiments were performed by exposing the vessels of anesthetized dogs, transversely piercing the vessel with the needle as near the mid-line as possible, drawing the ligatures through and loosely tying the free ends together. Three weeks later specimens were taken and examined.

In no instance was there occlusion of the lumen nor was there any evidence to indicate that the vessels would have subsequently become occluded through thrombus formation. In general the ligatures were found dividing the lumen and coated with a substance closely resembling the intima in gross appearance.

In the case of one artery and one vein, an ordinary occluding ligature was first tied about the vessel, after which a transverse suture was introduced about one centimeter on each side of the ligature. The results in these cases did not materially differ from those observed on the non-occluded vessels. No marked differences were observed with different kinds or sizes of sutures.

Microscopical results, particularly as regards the character of the deposit on the foreign surfaces and the presence or absence of intimal covering, will be reported later.

13 (632)

On tumor-immunity in rats (with demonstrations).

By **RICHARD WEIL.**

[From the Department of Experimental Therapeutics, Cornell University Medical School, New York City.]

It is the intention of the present paper to summarize briefly experiments bearing on the problem of the acquired immunity of rats to the implantation of tumors. In rats, as indeed in practically all the other species of animals in which similar experiments have been practicable, it has been found that the absorption of an implanted tumor is succeeded by a period during which the animal is refractory to further implantations. The same refractory condition can be induced by the injection of tumor autolysates (Levin), or by the injection of suspensions of normal tissue, or even of blood. The relative specificity and effectiveness of these procedures vary in their details; the underlying principle has been thought to be the same throughout.

In a series of experiments with the Flexner-Jobling rat tumor, I have observed certain phenomena which seem in a measure to support the belief that the mechanism of immunity to the tumor is identical in its biological manifestations with that found in infectious disease, and is therefore mediated by immune substances carried by the serum. These observations may be summarized as follows:

1. Inoculation of the Flexner-Jobling adeno-carcinoma into normals rats is not followed by any macroscopic evidence of

inflammation or reaction, if the grafts are made from a small, non-necrotic tumor.

2. Rats specifically immunized to the Flexner-Jobling adenocarcinoma respond to an implantation by an intense local inflammatory reaction, often with necrosis.

3. Animals bearing necrotic tumors present this reaction on reinoculation.

4. After removal of the necrotic tumor, the animal still reacts to reimplantation by local inflammation.

These phenomena seem analogous to those instances of local anaphylaxis known as the "Arthus" phenomenon in rabbits, and to the local allergic reactions described in human beings by Pirquet. Until the possibility of a reaction to a complicating infection of the tumor can be excluded (as suggested by Apolant of Yamanouchi's experiments), this interpretation must be considered provisional.

In the sarcomata of rats, it has not been possible to elicit these phenomena.

SCIENTIFIC PROCEEDINGS.

ABSTRACTS OF THE COMMUNICATIONS.

Forty seventh meeting.

*The Laboratory of Natural History, College of the City of New York.
February 21, 1912. President Morgan in the chair.*

24 (633)

The fermentation of carbohydrates and other organic media by streptococci.

By C. E. A. WINSLOW.

*[From the Department of Public Health, American Museum of
Natural History, New York.]*

The study of the fermentative powers of the streptococci has been carried out in England by merely noting the change of color in litmus media. In this country, Palmer and the writer, Broadhurst and Hilliard have used the more exact methods of titrating inoculated tubes and uninoculated controls, using phenolphthalein as an indicator and plotting the quantitative results obtained. The line of demarcation between fermenting and non-fermenting forms is drawn at the intermodal point between the peaks of the curve. A comparison of several hundred results obtained by English and American methods shows that the English method gives a uniformly higher proportion of fermenters, suggesting that a number of strains producing a very slight amount of acid and properly classed as non-fermenters, are recorded as positive by the English method.

A study of the correlations between action on different organic media shows that those substances tested may be arranged in a definite order of availability, such that a positive reaction in one medium usually implies that all those earlier in the series will be fermented, while failure to act on a given substance almost always implies that substances later in the series will not be fermented either. Among the streptococci dextrose comes first in order of availability, then the disaccharides, lactose and saccharose, and the glucoside, salicin (which easily yields a simple sugar). The

starch-like body inulin and the alcohol mannit come next and the trisaccharide raffinose is least available of all. This order corresponds to the size of the molecule, whereas in the *B. coli* group, the configuration of the molecule is the main thing, the aldehydic sugars being acted upon very readily, and the ketonic sugars less readily. The bacillus of the colon group which can utilize the ketonic disaccharide can almost always utilize the ketonic trisaccharide raffinose as well.

25 (634)

The comparative resistance of spores and vegetative cells of bacteria towards calcium hypochlorite.

By **C. M. HILLIARD.**

[*From the College of the City of New York.*]

At least three distinct grades of resistance to the disinfectant action of calcium hypochlorite may be recognized among the bacteria. They are respectively ordinary vegetative cells, acid-fast organisms, having a fatty composition, and the true spore cells. The present study is concerned only with the vegetative cell and the spore. Subsequent work will be done with the tubercle bacillus as representing the acid-fast group.

Pure cultures of *B. coli*, *B. prodigiosus*, *B. subtilis* (spore former) and *B. anthracis* (spore former) were grown in broth for a time sufficient for spores to appear in large numbers in the two latter cultures. A few drops were then transferred to dilution bottles, the initial number present was determined, and the calcium hypochlorite of known strength was added in carefully weighed amount. Agar plates were made at intervals and the reduction determined.

The results of the work to date may be summarized as follows:

1. The sterilizing action of calcium hypochlorite in water is very rapid at first, the maximum reduction being nearly complete in three hours.

2. Of the organisms studied, *B. subtilis* is most resistant, followed by *B. anthracis*, and then by the non-spore formers, *B. coli* and *B. prodigiosus*.

3. At least 1.5 parts of available chlorin to 1,000,000 parts

of water is necessary to get 99 per cent. reduction with a spore former in six hours, while 0.5 part to 1,000,000 is sufficient for this degree of reduction with non-spore formers.

4. Sixteen parts of available chlorin per million of water does not effect complete killing of *B. subtilis*; 1.5 parts brings about complete sterilization with *B. coli* and *B. prodigiosus*.

26 (635)

Studies on barium feeding.

By **C. L. ALSBERG** and **O. F. BLACK.**

[*From the Office of Drug Plant, Poisonous Plant, Physiological and Fermentation Investigations, Bureau of Plant Industry, Department of Agriculture, Washington, D. C.*]

Half-grown rats fed for some months on a mixed diet to which BaSO_4 was added remained in good health and did not store up measurable traces of barium in their tissues. However, when instead of a mixed diet one poor in calcium was fed, other conditions being the same, a few milligrams of barium were stored in the tissue of each animal. It is therefore evident that under special conditions even very insoluble substances may be absorbed to some extent.

27 (636)

The production of grafted and multiple embryos.

By **A. J. GOLDFARB.**

[*From the College of the City of New York.*]

After removing the fertilization membranes of sea urchin eggs (*Arbacea*) and allowing them to develop to the desired stage, the eggs were placed in an alkaline (NaOH) sea water and centrifuged in narrow bore tubes. In this way large numbers of eggs were agglutinated, and developed into double, triple, etc., blastulæ, gastrulæ and plutei. In ten to forty per cent. the eggs and blastomeres were more or less completely fused, forming giant blastulæ, composed of three, four or more eggs.

In the first group parallel development took place, resulting in double, triple, etc., embryos, many of which were subsequently separated by the antagonistic sweep of the cilia. In the second group, the eggs were more intimately united to form a common

blastocœle, common gut, or common body, within which the independent organs may or may not unite. When the embryos fuse slowly the contained organs appear to be antagonistic, for one is often absorbed completely, or the interaction results in a united but very atypic gut, skeleton, body, etc. The details of these changes are exceedingly interesting, but can be given only in the fuller publication.

28 (637)

The production of typical monstrosities by various means.

By **A. J. GOLDFARB.**

[*From the College of the City of New York.*]

Typical abnormalities have been produced by subjecting developing eggs to the action of certain salts, such as lithium chloride, and the implication, if not the conclusion has been made that a certain specificity obtained between these salts and the resulting abnormality. Herbst for example produced definite atypic gastrulæ, by subjecting sea urchin eggs to lithium chloride in sea water. Stockard produced definite atypic conditions of the eye and brain formation in *Fundulus*.

That the same results may be obtained in other ways seems to demonstrate that the extra-gastrulate condition of the sea urchin, for example, is due not so much to any specific action of the lithium chloride, as to a factor common to each of the following. Extra-gastrulate embryos were produced in fairly large numbers by such anesthetics as chlorotone and alcohol, by changing the concentration of the sea water in opposite directions, either by dilution or by concentration of the sea water, by the action of carbon dioxide and lastly various sugar solutions.

Similarly other well-defined atypic blastulæ, gastrulæ or plutei, though not always produced by each of these solutions, were found in many of them, thus giving color to the view that a disturbance once set up results in a typical reaction conditioned not so much by the nature of the disturbance as by the mechanism (the egg) involved.

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The percentage of water in the brain of the dog-fish.By **G. G. SCOTT.**

[From the Department of Physiology, Columbia University, and
Biological Laboratory of the U. S. Bureau of Fisheries,
Woods Hole, Mass.]

Donaldson ('10) has shown that in the albino rat between birth and maturity the percentage of water in the brain diminishes from 87.8 per cent. to 77.5 per cent. He calls attention to the fact that the human brain at birth contains a greater percentage of water than at maturity and from the investigations of Koch and Weisbach he obtains as the percentage of water in the human encephalon to be: Birth 88.3 per cent.; 2 yrs. 81.1 per cent.; 5 yrs. 79.2 per cent.; 25 yrs. 77.0 per cent. He concludes that probably in all mammals we will find the same range in percentage of water, that the loss in water occurs in the same manner but that the time required for each successive step is determined by the intensity of the growth process characteristic of each period. The present writer determined the percentage of water of the brains of 17 spiny dog-fish (*Squalus acanthias*) and 97 smooth dog-fish (*Mustelus canis*). The smooth dog-fish ranged in size from very small to large. There is no such reduction in the percentage of water as found by Donaldson and others in the case of the mammalian brain. The average percentage of water in all the *Mustelus* brains examined was 78.5 per cent. There was very little difference between this and that obtained for the very young or the old. There is an indication of a slight fall of about 2-3 per cent. between birth and maturity. The great reduction (*i. e.*, about 7 per cent.) occurs in mammals during the period when the central nervous system is growing most rapidly. Both the rat and man during this short post-birth period pass from a helpless state to one of activity. The rat is born helpless and blind, etc. The dog-fish is an active free-swimming organism at birth. The present writer would conclude then that the differences in reduction of water in the two cases is that the nervous (and body) changes which occur in the mammal are post-embryonic and extra-utero. In the dog-fish they take place in utero. Determinations from brains of late embryonic stages can only settle this hypothesis.

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The advantage for certain experiments *in vitro* of suspending trypanosomes in serum.

By **B. T. TERRY.**

[From the Laboratories of the Rockefeller Institute for Medical Research, New York, and from the George Speyer House, Frankfort a/M, Germany.]

The amount of trypanocidal substance contained in a given solution is sometimes estimated *in vitro* by determining the degree to which the solution may be diluted before it ceases to immobilize the parasites.

For want of a better diluent, trypanosomes have usually been suspended in physiological salt solution (with or without the addition of citrate), although salt solution not infrequently immobilized the parasites in 30 to 60 minutes.

In 1910, the writer made observations which caused him to substitute serum for the salt solution he had previously employed in suspending *T. brucei*. Serum (when not bound by the medication under investigation) had the following advantages:

1. The motility of the control parasites was greatly prolonged. This enabled the observations to be continued over a longer time.
2. The motility of the control parasites was accelerated. This enhanced the delicacy of the tests *in vitro* by rendering more striking the contrast between the poisoned and the non-poisoned trypanosomes.

It was found, moreover, that poisons not infrequently immobilized more quickly trypanosomes suspended in serum than they did those suspended in salt solution. This also seemed to give serum a slight advantage over salt solution as a medium in which to suspend trypanosomes.

Rabbit, ox, horse, goat, sheep, pig, chicken, rat, and mouse sera were tested and were found to be efficient in prolonging the motility of trypanosomes.

It soon became easy to keep on hand a large supply of serum, for experiment showed that cattle serum, filtered through a Berkefeld filter, bottled aseptically, and preserved in the ice-box, retained its activity for many months.

That the motility of trypanosomes is preserved longer in serum than in salt solution was noted years ago and has recently been emphasized by Schern,¹ but the writer is not aware that anyone has previously recommended suspending trypanosomes in serum for experiments *in vitro*.

31 (640)

The action of atoxyl.

By **B. T. TERRY.**

[From the Laboratories of the Rockefeller Institute for Medical Research, New York.]

The action of atoxyl is paradoxical. *In vivo* it is effective against certain parasites, *in vitro* it has little or no action. Ehrlich believes that the medicament must be reduced in the body before it becomes active. This view has been strengthened by Levaditi and Yamanouchi who have shown that emulsions of liver, muscle, and lung, when incubated with atoxyl, transform this medicament into a toxic substance. Levaditi apparently believes that the transforming agent is in the liver and other organs, while Yamanouchi concludes that it is in the red blood cells only. My results confirm much of the experimental work of Levaditi and Yamanouchi, but lead to a conclusion that, in its entirety, is apparently held by neither of these investigators.

In my experiments, both liver and blood when incubated with atoxyl (10 per cent.) at 37 degrees for 3 hours, transformed this medicament into a toxic substance.

The transforming agent in liver had characteristics, however, which in some respects were quite different from those of the active agent in blood.

The active agent in liver was soluble in salt solution, was filterable through collodium, and was quite resistant. Liver emulsion ground with sand in a mortar, or heated to 100 degrees for 10 m., lost little or none of its activity. The addition of blood to liver emulsion before incubation with atoxyl increased its activity, but liver emulsion washed *thoroughly* to free it of red blood corpuscles was inactive, probably because of the solubility of the transforming agent.

From the blood the active agent was apparently not extract-

¹ "Arbeiten aus dem kaiserlichen Gesundheitsamte," Berlin, 1911, xxxviii, 338.

able by salt solution. Moreover, it was very easily destroyed, soon losing all or nearly all of its activity if the blood was laked (*e. g.*, by the addition of distilled water or saponin, by prolonged shaking at 37 degrees, or by grinding in a mortar with sand and salt solution, or with sand and serum). It was almost completely destroyed by heating to 100 degrees for 10 minutes.

Conclusion.—Atoxyl is probably transformed into a trypanocidal substance in the living body both by the blood and by the liver (other organs were not tested). In tests *in vitro* the transforming agent in liver may be readily distinguished from the active agent in blood.

32 (641)

Parturient paresis and eclampsia. Similarities between these two diseases.

By **DANIEL J. HEALY** and **JOSEPH H. KASTLE.**

[*From the Laboratory of the Kentucky Agricultural Experiment Station.*]

In June, 1907, the attention of one of us (Healy) was called by Dr. M. A. Scovell, Director of the Kentucky Agricultural Experiment Station, to parturient paresis in the dairy cow. Dr. Scovell's intention was to have, if possible, the etiology cleared up.

It proved impossible to take up the problem until one year ago, and as our studies progressed, the similarity between parturient paresis and eclampsia became more and more evident. They are both intoxications which occur suddenly just before, during or immediately after labor. They are characterized by the same clinical features, namely, suddenness of onset, loss of consciousness, coma and similar febrile conditions. In both, the urinalyses are the most important clinical features, and the urinalyses in these two conditions are similar, namely, a disturbance of the nitrogen distribution among the compounds containing nitrogen, an increase of the ammonia excreted, the presence of albumen, and microscopically the presence of hyaline, granular and epithelial casts and blood cells.

The finer pathological changes occurring in parturient paresis have not been established, and as none of our cases died, we have not had the opportunity of studying these changes. However, we

have had ample opportunity to study the finer pathological changes in three guinea pigs which died in five, six and seven days under the influence of the toxin of parturient paresis. We have also observed these changes in another guinea pig, which received a smaller dose of the toxin, the dose not being sufficient to cause death in ten days and therefore he was chloroformed. The pathological findings in these guinea pigs correspond in every way to the characteristic lesions of eclampsia, namely, there was hemorrhagic necrosis of the liver, acute parenchymatous nephritis with interstitial hemorrhages, degeneration of the cells of the adrenal cortex, with interstitial hemorrhages, and destruction of the medullary portion. These experiments were fully controlled in every detail by means of guinea pigs injected with normal salt solution, fresh milk, fresh normal colostrum and fresh, normal, cow's urine. The control pigs all remaining alive and well at the present time, with the exception of the normal urine pig, which was chloroformed at the end of seven days and on post mortem found normal.

The modern treatment of parturient paresis is most remarkable in its result. The mortality has been reduced from 60 per cent. to less than 1 per cent. It was introduced by J. Schmidt, of Kolding, Denmark, and was based upon the theory that the disease was due to bacterial invasion of the udder. The treatment consists of acute dilatation of the udder by means of oxygen or sterile air.

That the disease is due to a toxin elaborated in the udder as the result of its own metabolism preceding normal milk production, there can be no reasonable doubt, and that the success of the modern treatment is due to preventing, by means of pressure, the absorption of this toxin, seems most highly probable.

We are of the opinion that eclampsia is due to a similar toxin, elaborated by the breast in a similar manner, and would strongly recommend, as the most promising treatment, dilatation of the breasts with oxygen or sterile air, or forcible compression of them by means of a properly applied bandage, after they have been emptied by means of the breast pump, and at the same time using whatever medical measures may be indicated.

We, ourselves, shall thoroughly test this method of treatment as soon as the opportunity occurs.

33 (642)

The toxic character of the colostrum in parturient paresis.By **JOSEPH H. KASTLE** and **DANIEL J. HEALY**.*[From the Laboratory of the Kentucky Agricultural Experiment Station.]*

Parturient paresis is preëminently a disease of plethoric heavy milking breeds of cows, and of those individuals which give the greatest yield of milk. Among the prime and immediate causes of the disease are parturition, a permanent or transient plethoric condition of the blood vessels, with corresponding increase of pressure on the nerve centers of the brain. The phenomenal trophic and secreting activity of the udder of the heavy milker and intense physiological activity of the mammary glands resulting in the sudden rise and absorption into the circulation of leucomaines or toxic alkaloids of the cells of the mammæ. These according to Law¹ are the principal causes operating to bring on an attack of this disease. In the present state of our knowledge it is of little moment whether we call the substances, other than milk, resulting from the sudden disintegrative changes in the udder at or about the time of parturition, leucomaines, alkaloids, toxins, or what not. It seems reasonably certain, however, that there is no gland of the size and physiological activity of the udder of a heavy milking cow, but what must contribute very largely and sometimes malignantly to the internal secretions of the animal.

The question, therefore, immediately before us in the study of parturient paresis and of eclampsia in the woman is to determine experimentally whether the udder and the breast, respectively, do under these acutely toxic conditions actually secrete poisonous substances, which if not quickly eliminated or prevented from entering the circulation might be held responsible for these diseases.

It therefore occurred to one of us, Kastle,² to test the conduct

¹ "Text-book of Veterinary Medicine," 2d ed. (1905), Vol. 3, pp. 301-317 Ithaca, N. Y.

² On the day after our three papers on parturient paresis and eclampsia were mailed to the editor of the *Journal of Infectious Diseases*, Chicago, viz., on February 13, 1912, Dr. Surface called our attention to an abstract by Helfer of a paper by Hoyois in the *Berliner Tierärztliche Wochenschrift*, October 5, 1911, No. 40, pp. 727-

of the first fresh colostrum of the cow obtained during an attack of parturient paresis, upon the lower animals. We have not yet been able to obtain a case of eclampsia. Accordingly eighteen experiments have been carried out on guinea pigs. These experiments have included a few other substances besides the first colostrum of a cow suffering from parturient paresis, by way of comparison, and these of course serve as controls on our other results. Up to the present, therefore, the following substances have been tested on the guinea pig, and in all instances were given intraperitoneally, by hypodermic injection, using 10 c.c. or in some cases less, viz., the first, fresh colostrum of the normal cow, fresh milk from a high-class dairy herd, the first urine of a cow suffering from parturient paresis, the urine of a healthy cow, normal salt solution, and aqueous solutions of the residue from colostrum and milk left after precipitating the same with dilute acetic acid and finally the first, fresh colostrum of a cow, obtained during an attack of parturient paresis. Briefly the following results have been obtained.

The normal salt solution, the urine of the healthy cow, and the fresh milk from the healthy herd produce no bad effects when injected intraperitoneally into guinea pigs. The first fresh colostrum of the normal cow produced diarrhea in the guinea pigs from which they speedily recovered and these pigs are now alive and well. The dried residue obtained by evaporating the filtrates from normal colostrum after precipitating with dilute acetic acid and neutralizing produced no effect.

Three female guinea pigs received 10 c.c. each, of the first, fresh colostrum of a cow in an attack of parturient paresis. (1) The whole colostrum, (2) skimmed colostrum, (3) colostrum cream. Pig 1 had no diarrhea, but died on the sixth day. On post-mortem this pig showed acute parenchymatous nephritis with interstitial hemorrhages, acute parenchymatous hepatitis with interstitial hemorrhages, acute degeneration of the cells of the adrenal cortex with complete destruction of the medullary

728, the original of which appeared in the *Annales de Med. Vet. de Bruxelles*, July, Aug., Sept., 1910, in which according to Hoyois the colostrum in cases of parturient paresis, on intraperitoneal injection in doses of 10 to 20 grams, caused paralyzing symptoms in rabbits and guinea pigs, with subsequent death at the end of seven to twelve days.

cells, and interstitial hemorrhages. No evidence of tuberculosis. Cultures from the liver, kidney and spleen showed no microorganisms. No peritonitis. The pig was not pregnant.

Pig 2 seemed well after the injection; had no diarrhea. Died at the end of five days. On post-mortem showed acute parenchymatous nephritis, with interstitial hemorrhage, acute parenchymatous hepatitis, with interstitial hemorrhage, and marked peripheral necrosis. Acute degeneration of the cells of the adrenal cortex, with complete destruction of the medullary cells and interstitial hemorrhages. No evidence of tuberculosis. The pig was in the very early stages of pregnancy. Cultures from the liver, spleen and kidneys negative. No peritonitis.

Pig 3 seemed well after injection and had no diarrhea. Aborted during first twelve hours after injection, fetus five and five tenths cm. in length. Died in six days. The post-mortem showed acute parenchymatous nephritis, with interstitial hemorrhages; acute parenchymatous hepatitis, with areas of complete necrosis and interstitial hemorrhages. Some degeneration of the cells of the adrenal cortex with complete destruction of the medullary portion, and interstitial hemorrhages. Acute lobar pneumonia of the left lung. No tuberculosis. Pig no longer pregnant. Cultures from the liver, kidney and spleen negative. Cultures from the pneumonic lung contained a diplococcus. No peritonitis except over upper and anterior surfaces of the liver.

A healthy male guinea pig received 10 c.c. of the first, fresh, clear urine of a cow ill with parturient paresis. This pig showed no discomfort and no diarrhea. It developed a very marked diuresis however, passing at least 200 c.c. of urine in 24 hours. This urine contained a small amount of albumin and no sugar. This pig recovered from the diuresis and seemed well, and was chloroformed on the 13th day. On post-mortem this pig showed parenchymatous nephritis with some interstitial hemorrhage, a rather extensive necrosis of the liver cells, but without hemorrhage, and also localized areas of necrosis in the adrenals.

It is evident from these results that normal salt solution, fresh milk, and the urine of a healthy cow cause no disturbances in healthy guinea pigs. The colostrum of the normal cow invariably produced a diarrhea when injected into the peritoneal cavity of

healthy guinea pigs. In this connection it is of interest to note that it has long been known that human colostrum acts as a mild cathartic on the suckling (Williams, "Obstetrics," 1908, 351-352). Otherwise no bad effects followed the administration of the normal colostrum of the cow to healthy guinea pigs. It will be seen from our results that death invariably resulted in guinea pigs from the intraperitoneal injection of the first, fresh colostrum of a cow in an attack of parturient paresis, and that the post-mortem examination of the organs of pigs that had died from this cause showed the same pathologic degenerations and changes that are shown by the organs of women who have died of eclampsia. Unfortunately but little is known regarding the micropathology of the cow in parturient paresis. We have shown, however, that cows recovering from an attack of this disease invariably show a nephritis which may, as the result of repeated attacks, become chronic.

Our results with the colostrum of a cow suffering from parturient paresis certainly go to show the presence therein of some substance or substances toxic to guinea pigs, and certainly point to the udder and the mammary glands as the place of origin of the toxins or internal secretions producing parturient paresis and eclampsia respectively. The fact that the urine of the cow with parturient paresis causes such a profound diuresis in the guinea pig, points to the presence of toxic substances even in the urine of animals so affected. A conclusion which is sustained by the results of the post-mortem examination on this particular case. We hope in the near future to attempt the isolation of the particular substance or substances in the colostrum or the udder, responsible for parturient paresis or at any rate, its more careful study and nearer identification. We would, therefore, reserve the right to continue these investigations along the lines indicated above with the object of throwing further light on the nature of the toxine contained in the colostrum of cows suffering from parturient paresis and also the possible occurrence of such a toxine in the colostrum of women suffering from eclampsia, and with the still further object of arriving, if possible, at the precise conditions under which these toxins are elaborated in the udder and mammary glands.

34 (643)

The internal secretion of the mammæ as a factor in the onset of labor.By **DANIEL J. HEALY** and **JOSEPH H. KASTLE**.*[From the Laboratory of the Kentucky Agricultural Experiment Station.]*

The importance of the internal secretions has come to be well recognized in modern physiology and medicine. Among other interesting observations in this field may be mentioned the fact that Miss Lane-Claypon and Starling (*Proc. Roy. Soc.*, 1906, B. 505) have shown that the stimulus to the hypertrophy and lacteal activity of the mammary glands, in pregnant animals, comes not from the ovaries, or the placenta or the uterus, but from the fetus itself. In connection with our studies on the toxic nature of the colostrum of the cow, ill with parturient paresis, we have succeeded in showing that the colostrum both of the normal cow and that of the cow ill with parturient paresis contain a substance, or substances, which have the power to bring on abortion in pregnant guinea pigs; and that neither normal salt solution (0.85 per cent. NaCl) nor the fresh milk of a healthy dairy herd have the power to bring on premature labor. It has also been shown that boiling for a short time does not destroy the power of the normal colostrum of the cow to accomplish premature labor in pregnant guinea pigs.

In this abstract of our paper on this subject we have only space for the details of one experiment, which are as follows:

Experiment 15.—A healthy guinea pig in the 5th to the 7th week of pregnancy received by intraperitoneal injection 10 c.c. of sterile, normal salt solution (0.85 per cent. NaCl). The injection caused no discomfort and at the end of five days she had not aborted. She then received by intraperitoneal injection 10 c.c. of fresh milk, from a healthy dairy herd. This was heated to 38° C. before the injection. The pig showed no discomfort and had not aborted at the end of four days. She then received, by intraperitoneal injection, 8 c.c. of the first, fresh, whole colostrum of a normal cow (second calf). This colostrum was heated to 38° C. before the injection. Following this last injection this

pig aborted in 60 hours, giving premature birth to two fetuses, each 6.5 cm. in length, and 60 hours after this she aborted a second time, giving premature birth to one fetus 7 cm. long.

It is evident from these results that the colostrum of the normal cow contains a substance, or substances, capable of causing a premature onset of labor in pregnant guinea pigs. This substance is also present in the colostrum of cows ill with parturient paresis. It resists boiling and is probably of the nature of a hormone. Our results bring to light a new and hitherto unrecognized correlation between the mammary glands and the uterus. According to Lane-Claypon and Starling the fetus through its internal secretions stimulates the hypertrophy and lacteal activity of the mammary gland. It is evident from our experiments that the internal secretions of the mammary gland stimulate the pregnant female to labor and the birth of the offspring.

35 (644)

Some vaso-reacting substances in blood serum.

By **J. P. ATKINSON** and **C. B. FITZPATRICK.**

[From the Department of Health Laboratories, New York City.]

These observations supplement our previous articles on serum digestive processes. All the reactions were obtained by the kymograph, the pressure in the carotid of the normal dog being recorded with a mercury manometer. The injections were made into the femoral vein. The normal sera (horse and rabbit) give a slight rise, whether freshly drawn or after standing for some weeks as far as we have observed.

The whole serum of a horse which had been injected with 800 c.c. of strong diphtheria toxin gave no reaction with the serum drawn the first three days after the injection. The serum of the 4th, 5th, and 6th day each gave depressions, when given in 8 c.c. volumes.

Another series of sera from the same horse, bled 6 weeks later gave well-marked depressions, with the sera drawn on the 3d, 4th, 5th, 6th, 7th, 8th and 9th day after the toxin injection.

Several specimens of refined antidiphtheria sera, some of which had given rise to rashes in humans, gave well-marked depressions.

These depressions are not caused by the injection of minute quantities of ammonium sulphate per se. A recent, whole, anti-pneumococcus serum, which produced rashes in humans, gave in a young dog well-marked depressions and after the total injection of 35 c.c. given in 7 c.c. volumes, there was a rise, 13 minutes after which the dog died. This depressor substance practically disappeared after four days standing in the ice-box.

We have noticed a similar rise after the injection of numerous 6 c.c. doses of beef extracts, each of which had produced marked depressions; we have however been unable to kill a dog with these injections. These observations would seem to indicate that the amount of depression per se within moderate limitations is not so important as the recoil or loss of recoil.

Three c.c. of nutrient peptone broth gave no depression. The blood sera of a rabbit, which had 5 days previously been injected with nutrient peptone broth gave splendid depressions in 6 c.c. volumes.

The blood sera of rabbits, which had been 5 days previously injected with heated, sterilized, cultures of the typhoid bacillus, pneumococcus, and streptococcus, gave remarkable depressions in 4 c.c. volumes.

The injection of $2\frac{1}{2}$ c.c. of the serum of a rabbit which died $4\frac{1}{2}$ hours after having received 1,000 m.l.d. of tetanus toxin intravenously, gave a decided depression.

The injection of $2\frac{1}{2}$ c.c. of the serum of a rabbit which had 3 hours previously received 1,000 m.l.d. of diphtheria toxin, intravenously, gave a depression. The depressor substance of both of these sera practically disappeared, after standing 6 days in the ice-box.

Adrenalin chloride prevents the depression caused by the tetanus depressor serum.

Twelve m.l.d. and 15 m.l.d. of diphtheria toxin gave no reaction when injected into the dog intravenously, 3 c.c. of broth containing 210 m.l.d. of diphtheria toxin gave a well-marked depression when injected intravenously into a dog which had been sensitized 24 hours previously with 100 m.l.d. of diphtheria toxin.

The blood serum of rabbits injected with 3 m.l.d. of diphtheria and tetanus toxins, drawn 4 days after the injections, gave marked depressions.

Contaminated sera cause depressions.

An antimeningococcus serum, which had produced rashes in humans caused well-marked depressions in $6\frac{1}{2}$ c.c. doses.

Serum of a diphtheria antitoxin horse, which was recovering from an attack of indigestion gave a slight depression. This serum was secured through the courtesy of Dr. Banzhaf.

These observations have extended over a period of $2\frac{1}{2}$ years.

Note.—We have already reported depressions from the injection of the sera of tuberculous rabbits and from the injection of tuberculins as well as from the injection of the sera of animals inoculated subdurally with normal and hydrophobic brain tissue emulsion.

36 (645)

A study by the Meyer method of the effect of blood serum and certain inorganic salts on surviving arteries.

By **E. A. PARK** and **J. C. JANEWAY**.

[Department of Medicine, Columbia University.]

The method employed is an adaptation of the Meyer ox carotid method. Instead of strips from the carotid, rings from the mesenteric or hepatic arteries of the ox strung in pairs were used, and from the coronary arteries as controls. Adrenalin, even in every dilute solution, constricts the former, while it causes the coronary to dilate, whether it be added to Ringer-Locke fluid, or to the ox blood serum. This method, then, based on the contrary effects produced by adrenalin on two kinds of arteries, each possessing a different reactive property to adrenalin, should be ideal for the detection of adrenalin and the separation of it from the confusion with other substances in the blood serum exerting a constrictor or dilator action. Ox blood serum as opposed to adrenalin produces a constriction of both coronary and mesenteric or hepatic arteries. Thus it essentially differs in its action from adrenalin. There is, then, so far as surviving arteries are concerned, a vasoconstrictor property of ox blood serum, not to be explained by the presence of adrenalin.

The constriction produced by ox blood serum on ox arteries

occurs abruptly after a latent period of only a few seconds and is comparable in its intensity to that produced by adrenalin on the mesenteric or hepatic arteries. The duration is at least four hours, the limit of our means for recording it. Passing oxygen through it weakens this constricting property, as does time, *i. e.*, allowing it to stand one or two days at room temperature. Adrenalin added to blood serum even at the height of a contraction further increases it in the case of hepatic and mesenteric arteries, but produces an especially marked relaxation in the case of the coronary artery. Adrenalin added to fresh ox blood to make a proportion of one to 800,000, we have identified thirty-six hours later; and when added to make a proportion of one to 100,000 after seven hours' oxygenation under a pressure of more than 100 millimeters mercury at incubator temperature.

Sodium chloride in dilution less than .01 produces a marked constriction of the above-named arteries as compared with Ringer-Locke fluid. The latent period is longer than that of adrenalin or ox blood serum, the ascent more gradual; moreover the height of the curve seems to vary inversely to the sodium chloride water ratio to a point .005, below which we have not investigated. At .013 sodium chloride the strips of artery apparently die. The relations of calcium and potassium to tonus have not been taken up yet. Barium chloride produces a vasoconstriction which exceeds that produced by adrenalin, or, so far as our experience goes, any other substance. The curve produced by it tends to be irregular, frequently assuming a staircase character.

37 (646)

The influence of the sugar concentration of the blood on the protein metabolism in phlorhizin diabetes.

By **A. I. RINGER.**

*[From the Department of Physiological Chemistry
of the University of Pennsylvania.]*

According to Rubner, the protein metabolism of a normal starving animal is composed of two fractions:

I. Wear and tear quota.

II. Dynamogenetic quota.

The first fraction represents the protein metabolized in the life processes of the cells. The second fraction represents the protein burnt for the purpose of maintaining the temperature of the body.

Landergren, however, presents considerable evidence to show that the "dynamogenetic quota" of Rubner is really the result of two distinct processes:

I. The protein that is metabolized for the increased production of sugar, in cases where sugar is absent from the diet and the glycogen supply becomes low.

II. For the maintenance of body temperature.

It is a well-known fact, that in phlorhizin diabetes, the protein catabolism rises enormously; in some cases as high as five times the starvation requirements. Because of the renal origin of the glycosuria, there is a constant tendency for the concentration of the sugar in the blood to fall. The following experiment was performed in order to test what part, if any, the concentration of the sugar in the blood plays in the regulation of the protein metabolism.

A dog was phlorhizinized in the usual manner, and the D:N ratio established. Seventy-five grams of glucose dissolved in water and divided into six doses were given *per os* on the fourth day of the glycosuria. 150 grams were given on the sixth day.

The results are here tabulated:

Dog No. 11.

Date.	Period.	Weight.	Total N.	Total Sugar.	D:N.	Remarks.
February, 1912						
15"	III.	17.53	14.40	52.08	3.62	
16	IV.	17.24	9.32	103.10	11.06	75 gm. of glucose given per os.
17	V.	16.86	14.00	50.95	3.64	
18	VI.	16.60	7.18	127.17	17.71	150 gm. of glucose given per os.
19	VII.	16.25	7.78	56.29	7.23	
20	Animal died under anesthesia, while a sample of blood was being withdrawn from the carotid artery.					

From the D:N ratio on the third and fifth days, we may assume that the phlorhizin intoxication was complete and that the protein burnt on the fourth, sixth and seventh days yielded 3.6 gm. of glucose for every gram of nitrogen.

The amount of glucose eliminated on the fourth day was 103.1 gm. By subtracting 33.55 gm., which originated from the protein (9.32×3.6), we find that 69.5 gm. of the 75 gm. of glucose fed, were eliminated unburnt. By applying similar calculations to the results obtained on the sixth and seventh days, we find that the protein metabolized during the sixth day yielded (7.18×3.6) 23.85 gm. of glucose, and during the seventh day (7.78×3.6) 28.01 gm. The total amount of glucose eliminated during these two days was 183.46 gm. By subtracting the glucose that was derived from the protein, we find that 131.6 gm. of the 150 gm. of glucose ingested were eliminated unburnt.

The nitrogen metabolism was diminished by a little more than 5 gm. on the fourth day and was reduced almost fifty per cent. on the sixth and seventh days. If the increase in the protein metabolism in phlorhizin diabetes were due to dynamogenetic reasons only, the burning of 5.5 gm. of glucose on the fourth day could not have spared the combustion of 31.8 gm. of protein. Nor could the burning of 18.4 gm. of glucose on the sixth and seventh days have spared as much as 81 gm. of protein.

From this experiment it is apparent that in phlorhizin diabetes, extra protein is catabolized in order to maintain the glucose concentration of the blood which, perhaps for some physico-chemical reason, is essential to the processes of life. The introduction of glucose into the system, although very little of it is burnt, spares that amount of protein.

It is also noteworthy in this experiment that the 150 gm. of glucose given within 12 hours were not eliminated completely during the first 24 hours, but were carried over to a great extent to the second 24 hours.

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The influence of glutaric acid on phlorhizin diabetes.

By **A. I. RINGER.**

[From the Department of Physiological Chemistry of the University of Pennsylvania, Philadelphia, Pa.]

Baer and Blum found that the subcutaneous injection of 10 gm. of glutaric acid had the power of greatly reducing the amount

of sugar and nitrogen in the urine of phlorhizinized dogs. The degree of reduction in the nitrogen elimination in most of their dogs is so marked (less than 1 gm. per 24 hours for dogs weighing 5.4 to 10.0 kilos!) that a repetition of this experiment seemed desirable.

Thanks to the kindness of Prof. Graham Lusk, I received 100 gm. of glutaric acid, which was prepared by Kahlbaum, and which enabled me to carry out the following research:

Dogs were phlorhizinized in the usual manner, and after establishing the D : N ratio, they received, subcutaneously, 10 gm. of glutaric acid dissolved in water and neutralized by means of NaHCO_3 . The glutaric acid was administered in three equal doses during the course of the day.

Dog No. 5.

Weight.	Total N.	Total Sugar.	D: N.	Remarks.
12.7	18.02	60.96	3.38	10 gm. glutaric acid.
12.2	21.07	70.32	3.33	
11.9	19.75	66.24	3.35	
Dog No. 7.				
13.87	16.92	63.05	3.72	10 gm. glutaric acid.
	17.86	65.54	3.67	

These results show that the glutaric acid, contrary to the findings of Baer and Blum, has no influence whatsoever either on the sugar or on the nitrogen elimination.

Another experiment was performed on a normal starving animal. It received 10 gm. of glutaric acid without showing any effect on the nitrogen elimination.

Baer and Blum report that a good many compounds containing two carboxyl groups possess the power of reducing the sugar and nitrogen elimination. Experiments are in progress to verify their contention.

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Influence of anemia and hyperemia on the growth of sarcoma in the white rat.**By M. J. SITTENFIELD.**

*[From the Department of Pathology of Columbia University,
College of Physicians and Surgeons.]*

From previous experimentation, it becomes evident that certain physiological and pathological factors on the part of the organism, as starvation, pregnancy, the feeding of various salts, racial differences, and so on, exert a decided influence upon the growth of transplanted tumor tissue. Moreschi in his experiments in 1909 concluded that under-feeding and starvation of the animal predisposes to retardation of the transplanted mouse carcinoma. Cluett, Mercier, and others have shown that during pregnancy the progress of the growth of the tumor which may be at a stand-still shortly before the ending of pregnancy, is very much lessened, and after labor and during lactation may even recede, *i. e.*, that the growth of one tissue exerts an unfavorable influence upon the artificially transplanted tissue growth of another.

Negré, Borrell's pupil, was able to control the percentage of takes by increasing or diminishing the salt contents of the fluids and tissues of the body. This proves conclusively that the subcutaneously transplanted tumor is dependent upon a great many, as yet unknown, conditions of the host, and also upon its metabolic changes.

The present experiments were undertaken with a view to studying the effect of tumor growth in a locally induced anemic and hyperemic condition in the white rat. The lower extremity of the rat was rendered partially anemic by ligation of the femoral artery at the saphenous opening, and a few hours subsequent, it was observed that the extremity became slightly paler than the opposite one, though there was no evident lack of circulation; and twenty-four, forty-eight, and seventy-two hours after this induced anemia, Ehrlich's rat sarcoma was inoculated subcutaneously into the leg. This experiment was performed on forty animals; of these thirty-three survived four to ten weeks,

and in only six animals, or eighteen per cent., did the tumor grow, and then only to a small size. The same number of controls were inoculated with seventy per cent takes.

To study to what extent anemia was present in these animals, several animals were killed, the blood washed out of both extremities by salt solution, subsequently injected with bismuth, and skiagraphed. These show that there is a marked difference between the vascular supply of the anemic leg, compared to the normal one.

Another set of experiments was performed to study the effect of passive hyperemia of the leg, induced either by rubber ligature, or by a bandage of adhesive plaster strips. A few hours afterwards, the leg became slightly swollen, grayish red, and the arteries still pulsating. This was continued for five to eight days, caution having been taken not to permit edema. Twenty-four hours after the onset of the hyperemia, twenty-five animals were subcutaneously inoculated in the leg with Ehrlich's rat sarcoma, and here the takes were ninety-six per cent.; and the tumor grew more rapidly and to a larger size than in the control animals, in which the takes were sixty per cent.

It is noteworthy that the anemic animals were subsequently inoculated subcutaneously and in only two out of twenty-nine did a growth result. It would seem, therefore, that these animals possessed an acquired immunity, probably from the absorption of substances from the first inoculation.

From these experiments it becomes apparent that partial anemia and passive hyperemia of the leg exert different influences upon the growth of the transplanted tumor, similar to the difference noted by Moreschi in his experiments of over and under feeding of his animals.

Goldman, in his experiments, has shown that the blood supply and the new formation of blood vessels are essential factors in the growth of a cancer cell.

Carl Levin, Bashford, and Gierke, have pointed out that the fibro-plastic and angeoplastic reaction on the part of the host are the deciding factors in the growth of a transplanted tumor cell, and it shall be the aim of subsequent experiments to further study the relation of the angeoplastic reaction on the part of the host in the anemic and hyperemic condition.

40 (649)

The elimination and toxicity of caffeine in nephrectomized rabbits.By **W. SALANT** and **J. B. RIEGER.***[Presented by permission of the Secretary of Agriculture.]*

In experiments on the elimination of caffeine in rabbits and guinea pigs carried out by the writers¹ in this laboratory recently it was found that much larger amounts of caffeine were recovered from the gastro-intestinal canal when these animals were fed oats than when carrots were given. Since greater quantities of urine are secreted on a diet of carrots than on one of oats, it seemed probable that the excretory function of the gastro-intestinal canal might be stimulated to greater activity in order to compensate for the diminished diuresis when oats were fed. The elimination of caffeine into the gastro-intestinal canal after the removal of both kidneys ought to be greater, therefore, than in normal animals.

In experiments which were performed with caffeine which was given subcutaneously to rabbits after double nephrectomy, the following results were obtained: The amounts recovered at the end of about 22 hours from the contents of the stomach and intestines varied between 7.7 per cent. and 11.78 per cent., which is two to three times greater than was found in normal rabbits, much larger amounts being present in the intestines than in the stomach. In one rabbit which died seven hours after caffeine was injected subcutaneously, about 10½ per cent. were recovered from the intestines and about half this amount was obtained from the contents of the stomach.

The total amount of caffeine eliminated in nephrectomized rabbits in about 22 hours was approximately equal to that eliminated by the gastro-intestinal canal and kidneys combined of normal rabbits during an equal period of time, thus showing that the stomach and intestines acquire much greater power of elimination after the kidney is removed.

Observations were also made on the toxicity of caffeine in nephrectomized rabbits. The results obtained showed that the resistance

¹ Bull. 157, Bur. of Chemistry.

is not less than in normal rabbits. In fact, it showed rather a tendency to greater resistance after the kidneys had been removed. Thus 100-150 milligrams of caffein per kilo failed to produce symptoms in nephrectomized rabbits. As was shown by the writers elsewhere,¹ 15 omilligrams per kilo injected subcutaneously into normal rabbits are usually toxic. A dose of 200 milligrams per kilo proved fatal to one rabbit, but two others survived with the manifestation of symptoms. It is interesting to recall in this connection that similar results were obtained several years ago by Meltzer and Salant² in experiments with strychnin in nephrectomized rabbits.

41 (650)

A quantitative study of the pupil dilatation caused by adrenalin.

By **DON R. JOSEPH.**

[*From the Department of Physiology and Pharmacology of the Rockefeller Institute for Medical Research.*]

In the normal rabbit, adrenalin given subcutaneously has no effect on the pupil; if given intravenously in fairly large doses there may be a dilatation lasting less than a minute. S. J. Meltzer and C. M. Auer have shown that after removal of a superior cervical sympathetic ganglion in rabbits, the pupil of the corresponding side dilates maximally upon the administration of adrenalin either subcutaneously, intravenously or by instillation. Their experiments were carried out from the qualitative point of view, that is, fairly large doses of adrenalin were used and a wide, long-lasting dilatation of the pupil on the gangliectomized side resulted.

I have recently made a quantitative study of the effects of intravenous injections of adrenalin on the pupil after removal of a superior cervical ganglion in rabbits. The object was to determine the minimal dose that will give a dilatation, and also the amount and duration of the dilatation produced by larger doses. The doses of adrenalin used per kilo animal, expressed in c.c. of the 1/1,000 commercial adrenalin solution, were 1/50, 1/30, 1/20, 1/10 and 2/10 c.c.

¹ Bull. 148, Bur. of Chemistry.

² *Jour. Exp. Med.*, 1901, Vol. 5, p. 643.

The results, stated briefly, are as follows: The average pupil-dilatation in six experiments with $1/50$ c.c. of adrenalin per kilo animal was 1.62 mm., with a beginning recovery from dilatation in four minutes, and a complete recovery in ten minutes.

In six experiments with $1/30$ c.c. there was an average dilatation of 2.25 mm.; recovery began in eight minutes and was complete in twenty-eight minutes.

In thirteen experiments with $1/20$ c.c., there was an average dilatation of 3.61 mm.; recovery began in six minutes and was complete in thirty-seven minutes.

In eight experiments with $1/10$ c.c., there was an average dilatation of 3.87 mm.; recovery began in ten minutes and was complete in forty-nine minutes.

Finally, in eight experiments the dosage was $2/10$ c.c. Here the average dilatation was 4.25 mm.; recovery began in twenty-five minutes, and was practically complete in an average of one hundred and eight minutes.

In other words, $1/50$ c.c. of adrenalin per kilo animal was practically the minimum amount that could be relied upon to give a definite dilatation; as the dosage of adrenalin was increased, the dilatation also became greater, remained at its maximum for a longer time, and the return to a normal diameter was slower.

42 (651)

Intermittent and continuous lights of equal intensity as stimuli.

By **G. H. PARKER** and **B. M. PATTEN**.

[From the Zoölogical Laboratory of the Museum of Comparative Zoölogy at Harvard College.]

It is generally assumed that white lights of equal intensity give equal stimulation. We have attempted to ascertain whether there is any observable physiological difference between the action of continuous white light and intermittent white light of equal intensity. From a common source of light two beams were conducted over separate paths of equal length to a common observation point. One beam passed through a narrow slit and was thus reduced to a continuous stream of light of low intensity. The

other beam was reduced by being passed through a revolving sector-wheel, thus giving rise to a succession of flashes and dark intervals which fused indistinguishably in the eye, producing the appearance of a continuous flow of light of low intensity. By adjusting the sector aperture and comparing the lights in a photometer, the two lights could be made physiologically equal. On measuring the physical intensities of the two physiologically balanced lights by means of a radiomicrometer, the intermittent light was found to be about 6 per cent. stronger than the continuous light. When the two lights were made equal from the standpoint of their physical intensity and were compared in a photometer, the continuous light appeared much brighter than the intermittent one. From these results we conclude that intermittent white light is a measurably less efficient stimulus than continuous white light of the same intensity, and that in this respect the action of the retina, like that of the photographic plate, affords an exception to the Bunsen-Roscoe law. The reduced efficiency of intermittent light is probably the result of chemical induction dependent upon the frequent interruptions of the light. The sector wheel (episcotister) is therefore an unreliable means for reducing the intensity of light.

43 (652)

Preliminary communication on the cytolytic action of ox-blood serum upon sea-urchin eggs, and its inhibition by proteins.

By **T. BRAILSFORD ROBERTSON.**

[From the Herzstein Research Laboratory and the Rudolph Spreckels Physiological Laboratory of the University of California.]

1. It has been shown by Loeb¹ that the eggs of sea urchins (*Strongylocentrotus purpuratus* and *Strongylocentrotus franciscanus*) may be fertilized by the blood-sera of mammalia, provided the eggs be previously sensitized by a brief immersion in a solution of SrCl_2 which is approximately isotonic with sea water.

2. I find that if ox-serum be rendered sufficiently potent by dilution (cf. below) the formation of a fertilization-membrane by

¹ J. Loeb, *Arch. f. d. ges. Physiol.*, 118, 36, 1907; 122, 196, 1908; 124, 37, 1908; "Die chemische Entwicklungserregung des Tierischen Eies," Berlin, 1909, p. 185.

the action of the serum is succeeded by cytolysis or may even be accompanied by marked agglutination of the eggs, thus confirming Loeb's view that the formation of a fertilization membrane is essentially a phenomenon of incipient cytolysis.

3. The cytolytic (and fertilizing) action of ox serum (rendered isotonic to sea water) upon sensitized sea-urchin eggs is enhanced by dilution with sea water, a maximum potency being attained at a dilution of about 1/16.

4. I find that the increase in the cytolytic activity of serum which accompanies dilution is attributable to the fact that the proteins in serum in some degree inhibit membrane-formation. The inhibitory effect of the proteins becomes negligible if these are sufficiently diluted. If a protein (*e. g.*, gelatin or ovomucoid) be added to diluted serum its cytolytic activity is greatly diminished or even abolished.

5. The inhibiting action of proteins upon cytolysis is due to the fact that they penetrate the outer membranes of the cells either with difficulty or not at all, so that by their osmotic tension they prevent the taking up of water by the cells. This is well illustrated by the fact that the order of efficiency of different proteins (the mixed proteins of serum, gelatin, "insoluble" serum globulin, casein and ovomucoid) is the reverse order of their ability to pass through the pores of a porcelain filter. The following table shows the concentrations of the various proteins investigated which were observed to permit or inhibit the formation of spherical membranes after treatment of the eggs with 50 c.c. of sea water containing $2\frac{1}{2}$ c.c. of *N*/10 butyric acid for $2\frac{1}{2}$ minutes and then transferring them to 50 c.c. of the protein solution in sea water:

Protein.	Highest Observed Concentration which Permits the Formation of a Spherical Membrane within $1\frac{1}{2}$ Hours.	Lowest Observed Concentration which Prevents the Forma- tion of a Spherical Mem- brane within $1\frac{1}{2}$ Hours.
	Per Cent.	Per Cent.
The mixed serum proteins.....	3.7	7.4
Gelatin.....	1.0	2.0
"Insoluble" serum globulin.....	0.3	0.6
Casein.....	0.25	0.5
Ovomucoid.....	0.125	0.25

6. It will be observed that the power of the mixed proteins of serum to inhibit membrane-formation is very strikingly inferior

to that of the other proteins investigated. On the other hand the CO_2 - or "insoluble" globulin of serum, when isolated and dissolved in sea water, is no less potent than other proteins in inhibiting membrane-formation. A 0.3 per cent. solution of the "insoluble" serum globulin very noticeably inhibits membrane-formation, and yet a 3.7 per cent. solution of the mixed proteins of serum, containing 0.33 per cent. of the CO_2 -globulin, under the conditions enumerated above only inhibits membrane-formation to a barely perceptible extent. These facts would appear to lend confirmation to the view advanced by Hardy¹ and myself² that the various proteins in sera are not present therein in the free condition, but bound together in a molecular complex.

44 (653)

Preliminary note.—The action of various agents upon the secretion of milk.

By ISAAC OTT, M.D., and JOHN C. SCOTT, M.D.

In these experiments we used the lactating goat, obtaining the milk by aspiration with a water bottle. We found, as Mackenzie has noted, an increased secretion from venous injections of extracts of the mammary gland. The boiled gland was also active. The pineal body, corpus luteum, and infundibulin were active after a previous dose of atropin. Atropin and antipyrin greatly decreased the secretion. Pilocarpin and digitalin augmented the secretion. Pilocarpin in large doses was active after a preliminary dose of atropin. Albumoses, peptones, and glucose increased the secretion. Sodium, potassium and calcium chloride increased the secretion. Eserine, muscarine, and nicotine did not augment the secretion. 1/1000 of a drop of infundibulin increased the flow of milk, and 1/100 of a drop caused a marked increase. Infundibulin is a 20 per cent. extract of the infundibular part of the pituitary body.

¹ W. B. Hardy, *Journ. of Physiol.*, 33, 251, 1905 (Appendix).

² T. Brailsford Robertson, *Univ. of Calif. Publ. Physiol.*, 4, 25, 1911; "Die physikalische Chemie der Proteine," Dresden, 1912, pp. 126-133.

45 (654)

Preliminary note on the pineal gland and the corpus luteum.By **ISAAC OTT, M.D.**, and **JOHN C. SCOTT, M.D.**

In a series of experiments we have found the pineal gland to have a marked diuretic action, previously noted by Eyster. At the time of each injection per jugular the volume of the kidney increases considerably, whilst, after a temporary fall, the pressure in the carotid shows some increase. About one half of one per cent. of glucose appears in the urine after the injection of pineal extract and after the use of corpus luteum.

Corpus luteum does not markedly change the pulse rate, but lowers blood-pressure 20-40 millimeters of mercury, and then it rises above normal for a short time. The intestinal peristalsis is markedly increased by corpus luteum.

In the pregnant uterus, corpus luteum increased the contractions.

46 (655)

The spleen and chronic constipation.By **ISAAC OTT, M.D.**, and **JOHN C. SCOTT, M.D.**

In the *Medical Bulletin*, 1897, one of us (Ott) stated, the spleen of all the animal extracts has the most marked effect on peristalsis. It produces the largest peristaltic waves. When the spleen was removed then peristalsis decreased. If now spleen extract was injected, then peristalsis was restored to a considerable extent above normal.

In 1908, Zuelzer (Dohrn, Marxer and Zuelzer, "Specifische Aufregung der darm Peristaltik, etc.," *Berliner Klinische Wochenschrift*, 1908, No. 48) with others confirmed the preceding results. He prepared an extract of the spleen, called "hormonal," for intravenous and intramuscular injection in man for the cure of chronic constipation. He reports marked success in this condition. This statement has been confirmed by Saar, Henle, Unger and several others.

We have tried the action of the Zuelzer extract of the spleen by the Magnus method. This consists in immersion of an excised segment of the intestine from an etherized animal in Ringer's solution through which oxygen is bubbling. The intestine is attached to a heart-lever and the contractions registered. The spleen extract showed a marked action. In another method a balloon was inserted into the small intestine of an etherized animal and the contractions registered by Albrecht's piston recorder. This method also exhibited an increase of contractions in the intestine. But they are not so marked as when a watery filtered infusion of the spleen was used.

47 (656)

The sequence of the protozoan fauna of hay infusions.

By **LORANDE LOSS WOODRUFF.**

[Sheffield Biological Laboratory, Yale University.]

1. In hay infusions, seeded with representative forms of the chief groups of Protozoa, there is a definite sequence of appearance of the dominant types at the surface of the infusion, *i. e.*, Monad, Colpoda, Hypotrichida, Paramœcium, Vorticella and Amœba.
2. The sequence of maximum numbers and of disappearance is identical with that of appearance, except that apparently the position of Amœba advances successively from the last (sixth) place to the fifth place and then to the fourth place.
3. A definite sequence of forms is not apparent at the middle or bottom of the infusions.
4. The middle of the infusions is tenanted chiefly by a free-swimming population brought there by an overcrowding at the top or bottom.
5. All of the protozoan forms considered (except Amœba) are chiefly surface dwellers and it is evident that when they pass their greatest development at the surface this maximum is seldom approached again, and their cycle is practically over.
6. The major rise and fall in numbers at the surface are usually about equally rapid, though the final disappearance of an organism may be long deferred.

7. The appearance of any of the protozoan forms under consideration, excepting *Amœba*, in appreciable numbers at the bottom is most often coincident with, or immediately subsequent to, its surface maximum, and portends its more or less rapid elimination as an important factor in the life of the infusion.

8. Numerous abnormal individuals and cysts are frequently to be found at the bottom in great abundance immediately after the surface maximum.

9. Emphasis is put upon the strictly biological interrelations (*e. g.*, those involving food and specific excretion products) of the various forms as the most important determining factors in the observed sequence.

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The experimental demonstration of the identity of so-called Brill's disease to typhus fever.

By **J. F. ANDERSON** and **J. GOLDBERGER.**

[*From the Hygienic Laboratory.*]

The rhesus monkey is susceptible to infection by inoculation with the blood from a case of "Brill's disease." One attack of the disease in the monkey induces a definite immunity to a subsequent infection with virulent blood of the same strain. Monkeys recovered from an infection with "Brill's disease" have been found to be immune to a subsequent infection with virulent blood from a case of Mexican typhus fever. Monkeys recovered from an infection with Mexican typhus fever have been found to be immune to a subsequent infection with "Brill's disease."

From the above results we conclude that the disease described by Brill is identical with the typhus fever of Mexico, and inasmuch as the New York strain is undoubtedly of European origin, we may also conclude that the typhus of Europe and the tabardillo of Mexico are identical. If this conclusion is correct, typhus fever has been present in New York City for a number of years and, according to verbal reports made to us, has occurred in other large cities of the United States. These results make the clinical recognition and study of typhus fever of increased importance and necessitate the exercise of appropriate prophylactic measures.

It is not intended to exaggerate the menace of this disease to the public health. Nevertheless, although the disease in New York City has apparently been mild and has shown little tendency to spread, it is apparently on the increase there and the possibility should be borne in mind that it may acquire virulence and epidemic prevalence.

49 (658)

The relation of the parathyroid glands to electrical hyperirritability.

By **HERBERT B. WILCOX.**

[From the Laboratory of Clinical Pathology of the College of Physicians and Surgeons, N. Y. C.]

The following observations were undertaken for the purpose of obtaining information as to the relation between parathyroid lesion and infantile tetany and of the value of the galvanic reaction as a diagnostic sign of the disease.

In all 25 operations were done on 18 dogs, tests being carried on during August and September, 1910, and from March, 1911, to the present time.

Information was sought on the following points:

1. The limits of response to be expected in peripheral galvanic stimulation of the normal dog.
2. The influence of age upon this galvanic response.
3. The comparability of electrical response in the dog to that of man.
4. The incidence of electrical hyperirritability and tetany following injury to or removal of 1, 2, 3 or all of the parathyroid glands.
5. The time of appearance of these evidences after operation.
6. The length of time by which the electrical evidences precede the physical signs of tetany in their appearance.
7. The constant or varying qualities of the changes of response to electrical stimulation.
8. The frequency of the presence of the electrical evidences of tetany when all other signs are absent.

9. The predisposition to more sudden and severe electrical irritability, when further parathyroid loss is suffered, by animals previously subjected to parathyroid injury.

10. The influence of gestation on the galvanic response of parathyropriva animals.

Technique.—Ether anesthesia.

Three procedures or a combination of the first two were followed.

1. The parathyroid gland or glands were exposed, lifted on the point of a needle and excised or crushed.

2. A thyroparathyroidectomy of one side was done.

3. A complete thyroparathyroidectomy was done on both sides and thyroid extract given to the dog.

For the galvanic tests the peroneal nerve-muscle group was used. The negative electrode was placed on the upper abdomen, the positive over the peroneal nerve as it passes around the head of the fibula. The instrument employed supplied a galvanic current from dry cells and was provided with a rheostat, polarity switch and balanced milliamperemeter measuring from .2 to 10 milliamperes.

Findings.—

1. In normal adult dogs K.C. is usually less than 2 m.a. and may vary between 1 m.a. and 3 m.a. A.C. is usual at from 3 to 5 m.a. It is seldom less than three and often greater than 5 m.a. A.O. is rarely obtained at less than 5 m.a. K.O. is never below 5 m.a.

2. Young puppies are less susceptible to galvanic stimulation than grown dogs. K.C. and A.C. alone are obtained at less than 5 m.a. Frequently K.C. alone is obtained and not often below 3 m.a.

3. Comparison of the findings on normal and parathyropriva dogs with over 300 observations on normal children and children having tetany shows that galvanic response is very similar in the two classes.

4. Of 4 dogs with one parathyroid gland removed, none developed frank¹ tetany. Two showed mild anodal hyperirritability

¹ By frank tetany is meant the development of tremors, muscular or laryngeal spasms, convulsions or paralyses.

during a period of 10 days following operation. One showed moderate anodal hyperirritability during a period of 7 days following operation. One showed no electrical change during 11 days after operation. The removal of one parathyroid resulted in only moderate lowering of the anodal reactions.

Of 8 dogs with 2 parathyroids removed none developed frank tetany. Two showed marked electrical hyperirritability to K.C., A.C., A.O. and K.O. during 25 days following operation. Two showed marked anodal irritability during 13 days and 10 months respectively after operation. Four showed very slight anodal irritability during periods of from 1 to 4 weeks after operation. Electrical irritability of varying degree follows injury to or removal of 2 parathyroid glands.

Of 2 dogs with 3 parathyroids removed neither developed frank tetany. Both gave prompt and marked anodal irritability with occasional low response to K.O. Observations were continued for 36 days after operation.

Of 4 dogs subjected to complete thyroparathyroidectomy at one operation, two gave complete hyperirritability on day following operation and developed tetany two days later. One developed marked anodal irritability with tetany the following day. One, for 46 days, showed neither electrical nor other symptoms of tetany.

Of 7 dogs having part of their parathyroid tissue removed at one time, and the remainder later, 5 developed prompt and complete electrical change and frank tetany. One showed no hyperirritability but died of tetany in six days after operation. One showed complete galvanic reactions but died on the sixth day without other signs of tetany. Prompt and complete hyperirritability, followed in from one to two days by severe tetany, resulted in the removal of all parathyroid glands.

5. Electrical change was noted in from 5 to 48 hours after operation. The promptness and severity of its development depended to a considerable degree upon the amount of parathyroid tissue removed.

6. In all dogs developing frank tetany the electrical diagnosis was established from 1 to 3 days before other symptoms appeared. Lesions which failed to produce tetany were usually accompanied

by electrical change. Marked hyperirritability was present in one case for 11 months without other symptoms of tetany.

7. Sixteen dogs at some time during their periods of observation gave response to all forms of current at less than 5 m.a. Seven dogs with all parathyroids absent were constantly low in all reactions. Five dogs, 2 with all glands removed, 3 with 2 removed, 1 with 3 removed, were constantly low in all but K.O. Four dogs, 3 with 2 glands removed, 1 with 3 removed, gave constantly varying reactions.

In one instance there was constant low K.C., high K.O. and great variation in the anodal tests.

As a rule the electrical change is sufficiently constant to make the test a valuable one. Variations are, however, to be expected.

8. Eight dogs, 2 with 1 gland, 4 with 2 glands, 2 with 3 glands removed showed marked and complete electrical hyperirritability without other symptoms of tetany. Parathyroid injury sufficient to produce hyperirritability does not necessarily result in frank tetany.

9. Eight dogs were subjected to parathyroid injury and later to further loss of glands. In each instance the electrical changes following second operation were more rapid in development and more severe than those noted after the first operation.

10. While under observation 2 parathyropriva dogs littered normally and 1 aborted at about 1 month. None developed tetany during gestation or lactation. There was moderate increased irritability during gestation which became more marked during lactation. No electrical change occurred in the animal which aborted.

SCIENTIFIC PROCEEDINGS.

ABSTRACTS OF THE COMMUNICATIONS.

Forty eighth meeting.

*Cornell University Medical College. April 17, 1912. President
Ewing in the chair.*

50 (659)

The influence of alcoholism on the offspring.

By **CHARLES R. STOCKARD.**

*[Department of Anatomy, Cornell University Medical College,
N. Y. City.]*

Two years ago I showed that almost all known gross deformities of the brain could be produced by treating developing fish embryos with alcohol and a number of anæsthetics.

Since that time these experiments have been extended to birds and mammals. The work of Feré with hen's eggs has been repeated and his results confirmed. When these eggs are subjected to the fumes of alcohol the shell is penetrated and the developing embryo is affected. The rate of development is reduced and a large number of monstrosities occur.

Guinea pigs have been put into a state of chronic alcoholism by treating them for six days per week with alcohol fumes to almost the point of intoxication. Forty full-term matings of various combinations have been made with these alcoholic animals. Treated males have been paired with normal females (test of paternal influence on offspring), treated females paired with normal males (maternal influence plus the direct effect on the developing embryo) and finally treated males and females were paired. The outcome of these matings has been most striking.

Twenty-five matings gave no result or the embryos were aborted early and eaten by the mother. Fifteen matings produced in all 25 young, of these two have lived to reach maturity and are apparently normal, four are still young but seem normal. Of the other 19, eight were stillborn or aborted shortly before

term, seven lived for a few days after birth and all died in convulsions, four were *in utero* when the mothers were killed and one of these was deformed.

All of the control matings were successful, all of the young lived and were vigorous.

51 (660)

Growth and maintenance on purely artificial diets.

By **THOMAS B. OSBORNE** and **LAFAYETTE B. MENDEL**.

[From the Laboratory of the Connecticut Agricultural Experiment Station, and the Sheffield Laboratory of Physiological Chemistry in Yale University, New Haven, Connecticut.]

[With the coöperation of the Carnegie Institution of Washington.]

In earlier reports of the authors' feeding experiments with isolated food substances¹ attention was directed to the failure to induce growth or secure prolonged maintenance of body weight in albino rats with any of the food mixtures tried prior to the introduction of "protein-free milk" as the adjuvant of the dietary which furnished the inorganic nutrients together with some of the carbohydrate (in the form of lactose). In order to determine whether the nutritive success achieved by the use of the protein-free milk was due to the peculiar supply of inorganic salts or some other ingredient, an artificial mixture of salts was prepared to imitate as nearly as possible the proportions of acid and basic radicals in the milk product. This mixture, the preparation of which will be described in detail in a forthcoming paper, contains: Ca 1.97; Mg 0.23; Na 2.03; K 2.66; PO₄ 3.33; Cl 4.13; SO₃ 0.30; Fe 0.04; citric acid 3.33; lactose 82.0 per cent. This purely artificial product added to purified proteins, starch, sugar and lard has already sufficed to meet the needs of rats for maintenance over very considerable periods of time, and has, thus far, proved as efficient in promoting early growth as the so-called protein-free milk used in our former experiments.

¹ Osborne, T. B., and L. B. Mendel, Carnegie Institution of Washington, Publication 156, Part II, 1911; and *Science*, 1911, XXXIV, p. 722.

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Feeding experiments with fat-free food mixtures.By **THOMAS B. OSBORNE** and **LAFAYETTE B. MENDEL.**

[From the Laboratory of the Connecticut Agricultural Experiment Station, and the Sheffield Laboratory of Physiological Chemistry in Yale University, New Haven, Connecticut.]

[With the coöperation of the Carnegie Institution of Washington.]

The question as to whether fats are, like proteins and carbohydrates, in some measure indispensable components of the diet has never been adequately determined. Stepp¹ has lately maintained that the so-called "lipoids," in distinction from true fats, are necessary for adequate nutrition. His experiments were conducted with mice. Following the methods employed by the writers² it has been possible to induce rats to grow at a normal rate with food mixtures containing only purified proteins, carbohydrates and inorganic salts. The problems suggested by the possibilities of this method of investigation are obvious.

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The masking of a Mendelian result by the influence of the environment.By **T. H. MORGAN.**

[From the Department of Zoölogy, Columbia University.]

As reported (Oct., 1911) a mutant of *Drosophila* appeared with a dominant sex-linked character, viz., abnormal abdomen. Typical Mendelian ratios are found in the F₂ offspring if an abundance of food and of moisture is present. As the culture grows older the flies that emerge later gradually change over to the normal type. As a result the Mendelian ratio completely disappears from the surface phenomena. That Mendelian inheritance has actually occurred, but is temporarily masked, is shown by testing the F₂ flies, when the expected number is found (under wet

¹ Stepp, *Zeitschrift für Biologie*, 1911, LVII, p. 135.

² Osborne, T. B., and L. B. Mendel, "Feeding Experiments with Isolated Food-Substances," Carnegie Institution of Washington, Publication 156, 1911.

conditions) to transmit the abnormal abdomen. This is best demonstrated by linking the factor for abnormal abdomen *A* with another sex-linked factor, such as the *b* factor in the yellow mutant, or the *c* factor in the white mutant, or to both together as in the two examples given below.

$$\begin{array}{l}
 YRA \sigma \\
 GWN \varphi
 \end{array}
 >
 \begin{array}{l}
 GRA \varphi \\
 GWN \sigma
 \end{array}
 =
 \left\{ \begin{array}{lll}
 GRA \varphi & 95 & 56 & 3 \\
 GRN \varphi & 0 & 4 & 32 \\
 GWN \varphi & 88 & 49 & 34 \\
 GWN \sigma & 98 & 49 & 19 \\
 YRA \sigma & 81 & 47 & 7 \\
 YRN \sigma & 1 & 2 & 25
 \end{array} \right.$$

$$\begin{array}{l}
 YRN \varphi \\
 GWA \sigma
 \end{array}
 >
 \begin{array}{l}
 GRN \varphi \\
 YRN \sigma
 \end{array}
 =
 \left\{ \begin{array}{lll}
 GWA \sigma & 50 & 21 & 9 \\
 GWN \sigma & 1 & 24 & 24 \\
 GRA \varphi & 76 & 3 & 0 \\
 GRN \varphi & 5 & 49 & 60 \\
 YRN \varphi & 45 & 93 & 61 \\
 YRN \sigma & 49 & 29 & 30
 \end{array} \right.$$

The tables show that in the expected classes for abnormal abdomen *A* this character at first appears but later is replaced by the normal character *N*. When the normal flies (of the last sort) were tested they were found to transmit abnormality. The other classes that are genotypically normal remain so in the next generation. Cultures that had produced only abnormal flies for nine generations under wet conditions were allowed to dry out when all the later-hatched flies became normal. These were then placed under moist conditions, and all of their offspring were as abnormal as their ancestors had been.

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Sources of error in serological work.

By **WILFRED H. MANWARING.**

[From the Rockefeller Institute for Medical Research.]

I have been engaged for some time in attempts to determine the approximate chemical nature of certain bactericidal substances obtained from horse leucocytes. My earlier attempts to isolate and identify these substances were characterized by inconstant and inconsistent results. This led to an examination of the

experimental method, with the discovery of certain sources of error not usually taken into account in serological work.

The first source of error is the possibility of there being marked changes in the chemical composition of serological substances as a result of changes in concentration. The bactericidal substance with which I was working is fairly stable. It can be heated to 60° C. for an hour without loss of bactericidal power and can be stored in the ice chest for weeks with but slight deterioration. The substance can be passed through a series of chemical manipulations, involving such processes as salting-out, dialyzing, evaporating to dryness, and redissolving, and can be recovered quantitatively from the final product of such manipulations, provided the volume of fluid in which it is dissolved is at no time allowed to increase much above the original volume from which the substance was obtained. If the volume is allowed at any stage to materially increase, there is brought about a rapid deterioration of the bactericidal substance at that stage, giving a final product without bactericidal action.

The second source of error is the possibility of there being marked changes in the specific properties of serological substances as a result of variations in the amount of sodium chloride with which they are mixed. The purified bactericidal substance from horse leucocytes, dissolved in distilled water, has about half the bactericidal power of the initial crude product. If dissolved in physiological saline solution, instead of in distilled water, it is without bactericidal power.

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The relation of the virulence of the tubercle bacillus to its persistence in the circulation.

By **ALFRED F. HESS.**

[From the Research Laboratory, Department of Health, New York City.]

It seems as if the tubercle bacillus offered an exceptional opportunity to study the question presented in the title of this study. As is well known, one type of the bacillus, namely, the human type, is non virulent for the rabbit, whereas the bovine type causes

a general tuberculosis in this animal. Accordingly experiments were instituted in the following manner: four rabbits were injected for each test, two with a human type of bacillus, the other two with the bovine type, in each case 1/100 mg. and 1 mg. of a culture being injected into the ear vein. These four animals were bled one half hour, one hour, two hours, and three hours after injection, 5 cu. cm. being caught in a solution of sodium citrate. There were thus eight specimens taken from the two rabbits inoculated with the human tubercle bacillus, and eight from the two inoculated with the bovine bacillus. These sixteen specimens were injected into as many guinea-pigs, and after six weeks these animals were examined for tuberculosis.

In all, six experiments of this description were successfully carried out, using twenty-four rabbits and 112 pigs. In the tuberculosis test, 44 of the pigs injected with "bovine blood" survived, 26 of these, that is, 69 per cent., were found tuberculous. Of 45 of those injected with the human virus 7 developed tuberculosis, that is, about 18½ per cent. In almost all of these experiments the bovine bacillus was found more frequently in the circulation than the human type of bacillus. This was not the case to any great extent in two of the experiments, where the bovine strain was not of marked virulence.

The conclusion is, therefore, that a certain parallelism exists between the virulence of the tubercle bacillus and its persistence in the circulation of the rabbit. The more virulent bovine organism remains in the circulation more constantly and for a longer period than the less virulent human type. The cause of this difference is being studied at present. Perhaps we can generalize from this fact in the case of other microorganisms.

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On indican in the blood of uremic patients.

By **NELLIS B. FOSTER.**

[From the medical service of the New York Hospital and the Laboratory of Biological Chemistry, Columbia University, at the College of Physicians and Surgeons, New York.]

A demonstration of the constant presence in uremic blood of an abnormal aromatic body such as indican would be highly signifi-

cant since this would be suggestive of the nature of the abnormal metabolism. Hence a recent report¹ to the effect that indican is present in the blood in uremia invited confirmation, and especially as the amounts present are stated to be sufficient to give the ordinary blue color with chloroform when only 10 c.c. of serum are used for the test. Considering the total volume of blood this would mean an enormous concentration.

The method for detecting indican employed by Obermayer, was, in brief, to separate all of the proteins from the serum by means of alcohol, which after filtration is evaporated on the steam bath. The residue from the alcohol filtrate is taken up in water, freed of salts with lead acetate and the latter in turn removed by sodium phosphate. A water clear filtrate is the final result which is tested by the usual method employed for urine with Obermayer's reagent.

In repeating Obermayer's experiments the method above mentioned was used, also the separation of the proteins was conducted by means of phosphotungstic and hydrochloric acids and in a third series a method was used which is based on that of Rona for the precipitation of colloids in blood, by means of kaolin. The clinical material consisted of ten typical cases of uremia, all of the convulsive type. It was noted that indican could not be detected in fresh serum when 10 c.c. was used for tests; with larger amounts, 25 c.c., a questionable coloration of the chloroform resulted in one instance. If instead of using fresh serum or blood, the material be allowed to stand twenty-four to thirty-six hours many of the uremic bloods then gave a fairly definite reaction. When the kaolin method of separation of proteins is employed, however, no indican could be detected even though the equivalents of as much as 50 c.c. of blood be used for the test.

¹ Obermayer and Popper, *Zeitschr. f. Klin. Med.*, 1911, 72, pp. 333-72.

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The inhibitory action of adrenalin in muscle-pancreas mixtures.By **ALWIN M. PAPPENHEIMER, M.D.**

[From the Department of Pathology, College of Physicians and Surgeons, New York City.]

Much evidence has accumulated since Blum's discovery of adrenalin glycosuria in 1901, to indicate an antagonistic action between the adrenal and the pancreas in carbohydrate metabolism. The more intimate nature of this antagonism is still obscure. Bayer in a recent article has suggested three possible modes of interaction:

1. The action of the internal secretion of the pancreas may be directly inhibited by the adrenalin, or
2. The secretion of the pancreatic hormone may be prevented, either directly or through reflex nervous influence, or
3. The adrenalin, through its vaso-constrictory action, may close up the channels of exit through which the internal secretion of the pancreas reaches the circulation.

At the suggestion of Professor MacCallum, the attempt was made to demonstrate this antagonistic action between adrenal and pancreas in vitro, where the problem is simplified by the exclusion of secretory or vaso-motor influences. The technique used was, with slight modifications, that described by Cohnheim in 1906 for the demonstration of the activating effect of pancreas extract upon the glycolytic ferment of muscle. The finely hashed muscle of cats was extracted in iced sodium oxalate solution, the excess of oxalate precipitated with calcium chloride, and glucose added in known amount. Duplicate flasks of muscle extract alone, of muscle extract plus pancreas, and of muscle extract plus pancreas plus adrenal gland extract or adrenalin in varying dilutions up to 1 in 110,000, were incubated overnight at 37° under toluol. Sugar determinations were made with Benedict's solution from samples taken before and after incubation.

It was found that the addition of adrenalin to muscle-pancreas mixtures prepared in this way, gave a higher sugar content than the controls. This effect was obtained definitely in 9 out of 10

experiments. In 6 of the 10 positive experiments, there was an actual increase in the amount of reducing substance during the course of the experiment.

The results may be summarized as follows:

Mixture.	Average Loss of Reducing Substance.
Muscle-extract alone.....	- 0.096 gm. in 100 c.c.
Muscle-pancreas.....	- 0.225 gm. in 100 c.c.
Muscle-pancreas-adrenalin.....	+ 0.01 gm. in 100 c.c.

These experiments then show that the antagonistic action between adrenalin and pancreas, as schematized by Falta, Eppinger and Rudinger, may be demonstrated in vitro independently of any possible nervous influence. King in 1910 showed that a similar retarding influence upon the disappearance of reducing substance in muscle pancreas mixtures was exerted by thyroid extract.

The question as to whether there occurs in this reaction, a true glycolysis, or as Levene and Meyer hold, merely a condensation of the sugar molecule, is left untouched by these experiments. The antagonistic action of adrenalin and pancreas in regard to the disappearance of reducing substance in muscle extracts seems to be clearly demonstrated.

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The characteristic course of the rise of blood pressure caused by an intraspinal injection of adrenalin.

By **J. AUER** and **S. J. MELTZER**.

[From the Department of Physiology and Pharmacology of the Rockefeller Institute.]

An intravenous injection of adrenalin causes a rapid steep rise of the blood pressure with a gradual fall. An intramuscular injection produces a similar effect. A subcutaneous injection either produces practically no effect or it causes a very slow rise which rarely exceeds fifteen millimeters. In recent years adrenalin was injected into the spinal canal in conjunction with some local anesthetic. The question as to the nature of the effect of these injections upon the blood pressure has to our knowledge never yet been investigated. On the basis of the generally accepted assumption that the absorption from the spinal canal into the circulation

is not very prompt we might expect that the intraspinal injection of adrenalin will have no stronger effect upon the blood pressure than that of a subcutaneous injection. We studied this question experimentally and may say at the outset that our results did not bear out this anticipation. Our experiments were made on six monkeys, using each monkey two or three times. The amount injected was either 1 c.c. or 1.5 c.c. of the commercial adrenalin. Most of the injections were made in the lumbar region; but in a few instances the adrenalin was injected in the thoracic region in the fifth intervertebral space. During the experiments the animals were under fairly profound anesthesia and we are unable to state whether the injection had any other effect besides the change in the blood pressure. But it is important to point out that even doses of 1.5 c.c. of adrenalin had no recognizable after-effects upon the animal.

The action upon the blood pressure was in most cases very characteristic. The pressure would begin to rise slowly but steadily, so that in a few minutes it would reach a maximum varying between 150 and 190 millimeters, and would then commence to go very gradually down. As a rule the entire course of the rise lasted longer than in intravenous injections, in some instances even longer than half an hour. The fall of blood pressure occurred so slowly at times that the original level was not reached during the entire time of observation, a fact which might be of considerable practical importance.

Twenty-one injections were given to these six monkeys at intervals; of these thirteen gave the typical rise described. In six cases the rise was preceded by a moderate fall (9-52 mm.) of short duration ($\frac{1}{2}$ -4 minutes) and in one case this fall was the only effect of the injection. In the seven instances the injection brought on a rise similar to that of an intravenous injection but of longer duration. It is possible that in these cases part of the injection entered indeed into a vein.

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Demonstration of vomiting movements in an eviscerated animal under the influence of digitalis.By **C. EGGLESTON** and **R. A. HATCHER.***[Laboratory of Pharmacology of Cornell University Medical College.]*

It is commonly accepted that apomorphine produces emesis through its action on the center in the medulla concerned in emesis, but that digitalis produces emesis through its irritant action on the stomach.

We had some evidence that digitalis produced vomiting through its central action and decided to carry out as many experiments as possible of those which had been made in establishing the seat of action of apomorphine, but substituting digitalis, and in the course of the investigation we utilized a method which has not been described hitherto, and which consists in the removal of the gastro-intestinal tract from the esophagus to the anus, after tying the vessels which supply the tract, and injecting digitalis intravenously after an appropriate interval of time, varying from a few minutes to an hour and a half.

We have produced vomiting movements in about fifty per cent. of the experiments so made, and nausea in all but one of the others, and barring those experiments where the depression from the operation seemed to indicate that nausea could not be induced, the percentage of successful experiments is still higher.

Using apomorphine intramuscularly, we have been able to produce vomiting movements in nine out of ten such experiments on the dog.

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The variations of pressure in the pulmonary artery.By **CARL J. WIGGERS.***[From the Physiological Laboratory, Cornell University Medical College, New York City.]*

The systolic and diastolic pressures existing in the pulmonary artery of naturally breathing dogs have not been heretofore investigated. By means of a sensitive pulse pressure instrument

capable of standardization against maximal and minimal valves,¹ it has been possible to fill this gap in the physiology of the circulation. The operative technic was so adapted that (1) normal intrathoracic pressure relations during inspiration and expiration were obtained when the records were taken, (2) artificial pressure changes in the intrathoracic cannula and manometer tubes were obviated, (3) clot formation was minimized and recognized when present, (4) only a small portion of the pulmonary circuit was occluded, and (5) the systemic and right auricle pressures corresponded to that habitually found in animals.

The results of 13 such experiments showed that, during quiet normal breathing the systolic and diastolic pressures fell during inspiration and rose during expiration. The systolic pressure averaged 43.3 mm. in expiration and 31.7 mm. in inspiration, the diastolic pressure 20 mm. in inspiration and 11.9 mm. in expiration. In experiments where the heart rate ranged from 180 to 25 per minute, it was found that the diastolic pressure *decreases* as the heart rate is reduced. The same holds true for the systolic pressure between heart rates ranging from 180 to 100 or 80 (the latter figure varying in different animals). When the heart becomes still slower the systolic pressure again increases.

During temporary apnea vagi, the maximal pressure dropped 40 to 32 per cent., the minimal pressure increased 10–25 per cent. over that occurring during natural breathing, showing that respiratory movements determine to a pronounced extent the extreme pressures in the pulmonary artery.

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The results of ligation of the pulmonary and cutaneous arteries in the frog.

By **T. S. GITHENS.**

[From the Department of Physiology and Pharmacology of the Rockefeller Institute for Medical Research.]

The frog possesses, in the lungs and the skin, two organs for the purpose of respiratory exchange, and it has long been estab-

¹ Wiggers, *Journ. Exp. Med.*, XV, 1912, p. 174.

lished that the skin respiration suffices for his needs at low temperature.

I have attempted to produce asphyxia in frogs by ligating the vessels which carry blood to the lungs and to the skin. It may be well to mention here certain anatomical data. The truncus arteriosus rises from the heart of the frog and divides into a right and left branch which each give off three branches, the carotid, the aorta and the pulmocutaneous. The last divides into two, one of which goes to the lungs and the other, the cutaneous, supplies the skin of the entire trunk. A large branch from the carotid makes a free anastomosis with the cutaneous artery.

At temperatures below 20° C. the frog requires very little gas exchange and I found that ligation of the pulmocutaneous and anastomosis was not sufficient to produce asphyxia, although it deprives the frog of the lungs and most of the skin, leaving only the mucous membrane of the mouth and the skin of the legs for respiratory purposes. If in addition the mouth was excluded, by ligation of the carotid arteries, thus leaving only the skin of the legs, the frogs died in 2-3 days. If the lungs and entire skin were excluded by ligating the pulmocutaneous and the iliac arteries death occurred in about 36 hours in spite of the respiratory exchange through the mucous membrane of the mouth. Frogs in which the respiration of the lungs and mouth was absolutely prevented by keeping them under water, but in which the entire skin was available, lived indefinitely at this temperature.

With an increase of temperature to 28° frogs in which the cutaneous respiration was entirely excluded by ligation of the cutaneous and iliac arteries were still able to live indefinitely. If the lungs and skin of the body were excluded by ligation of the pulmocutaneous and anastomosing arteries, death occurred in about 24 hours, and if the skin of the legs was also excluded by ligation of the iliac arteries, in about 12 hours. If the pulmonary and buccal respiration was prevented by keeping frogs under water, no asphyxia was noted during the five hours of the experiment, but frogs in which the cutaneous arteries were tied and which were kept under water died within 3 hours.

At a temperature of 34°, asphyxia could be caused by excluding the cutaneous respiration. Frogs in which the cutaneous and

anastomosing branches were ligated lived only about 8 hours. If the lungs and most of the skin were excluded by tying the pulmocutaneous and anastomosing arteries, the frogs lived about 6 hours and if the mouth also were excluded by sewing this and the nostrils shut and tying the cutaneous arteries, they lived about $4\frac{1}{2}$ hours. Control frogs kept at this temperature, showed no deviation from normal excepting slight over-excitability.

These results show with how little gas exchange frogs can live and also the large factor of safety with which their respiration is normally provided. Auer and Meltzer have recently shown that dogs could live with a supply of oxygen only one tenth of that which they normally consumed.

The results also show the great increase in the requisite gas exchange with rise of temperature and the inability of the skin respiration of the frog to support life at even moderately high temperatures, at which the lungs and mouth alone are still sufficient.

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Variations in the response of different arteries to blood serum and plasma.

By **HUGH A. STEWART** and **SAMUEL C. HARVEY.**

Recent work by Brodie, Sollmann, and O'Connor has shown that the blood contains substances acting on the vasomotor apparatus other than suprarenin. Even before the work of these investigators it had been noticed by Stevens and Lee that the use of defibrinated blood for the perfusion of isolated organs was often unsatisfactory because of the gradual diminution in outflow. This was not investigated thoroughly until 1900 by Brodie. He observed that the injection of blood serum into the jugular vein of a cat caused an immediate fall in blood pressure. The cat's own serum was as efficient in this respect as the serum of any other animal. The cat, however, is the only animal which responds in this manner, for Brodie's experiments were negative on the dog and rabbit. The mechanism in this case appears to be a reflex inhibition of the vasomotor center from excitation of the pulmonary branches of the vagus. The importance of Brodie's work lies in the fact that he was the first to show that plasma and

serum are not identical in their physiological activities, for, whereas the effect just described is produced by serum, plasma is entirely inactive. The process of clotting liberates some substance to which this action is to be attributed.

It was probably these experiments of Brodie which guided O'Connor in the analysis of the constrictor effect produced by blood serum on the hind limbs of the frog. He was able to show that the constriction produced by serum is not entirely due to its suprarenin content. Another substance comes into play which causes constriction and which is present only in the serum.

We have investigated the vasomotor effect of plasma and serum in different vessels of the body, especially in regard to their mode of action.

The methods we employed were the perfusion of the organ with Ringer's solution in a moist atmosphere at the temperature of the body and under a constant pressure. The outflow from the vein was recorded with a signal magnet writing on a smoked paper. Two c.c. of serum or hirudin plasma were injected close to the canula inserted in the artery.

Effect of serum.—The typical effect when injected into the vessels of the limb is to produce an immediate diminution in the rate of outflow. This usually lasts for from five to ten seconds, when it gradually begins to return to normal. The original rate of flow is regained in about five minutes.

A similar result is obtained when the heart is perfused.

Entirely different is the effect which is produced when 2 c.c. of serum are injected into the vessels of the perfused kidney. Instead of a vasoconstriction there is produced a pronounced vasodilatation.

We have first to determine whether the dilatory effect on the kidney and the constrictor effect on the limb vessels are due to the same substance. It can readily be shown that two substances are operating. If the serum is boiled and filtered through a Berkefeldt filter and injected we now get no dilatation of the kidney vessels, but instead a constriction.

As before, the effect of boiled serum is to produce a constriction of the limb vessels.

Precipitation of the protein constituents of serum by alcohol

and the injection of the dried filtrate dissolved in Ringer's solution retains the constrictor substance, but it contains no vasodilator for the kidney vessels.

We are, therefore, led to the conclusion that serum contains a constrictor substance which acts on the limb vessels, the kidney vessels and the coronaries. In addition there is also present a dilator substance acting specifically on the renal vessels. The dilator substance is a proteid, the constrictor substance is not. The perfused kidney after the injection of serum is subject to the action of both a dilator and a constrictor substance. The dilator is the more powerful and masks the action of the constrictor. The constrictor substance becomes manifest after removal of the dilator by boiling or by precipitation by alcohol.

Is the constrictor substance described above the suprarenin quotient of serum? Suprarenin, as is well known, causes constriction by stimulation of the sympathetic nerve fibers. If we add apocodeine hydrochloride to the perfusion fluid we can paralyze the sympathetics and in this way render the preparation insensitive to the strongest solutions of suprarenin. If, however, we inject serum there is still produced almost as great a diminution in the rate of outflow as before. We have thus evidenced that the constrictor substance is not suprarenin, and further, that it is a body which acts directly on the muscle coats.

In regard to the dilator substance acting on the kidney we have found that it still causes an increased outflow after the injection of serum when the perfusion fluid contains apocodeine.

Effect of plasma.—Plasma differs markedly in its action. If hirudin plasma is injected into the vessels of the limb it produces a much less constriction than does the corresponding amount of serum. This result is dependent only upon the amount of suprarenin it contains, for when the sympathetics are paralyzed the injection of serum produces no change in the rate of outflow.

On the kidney vessels, however, plasma produces an even greater dilatation than does serum.

The conclusions which we have been able to draw from these experiments are as follows.

1. That in both plasma and serum there is present a substance which causes dilatation of the renal vessels. This substance is a proteid.

2. That the process of clotting liberates a vasoconstrictor substance which acts on the coronaries, the renal vessels and the limb vessels. It acts directly on the muscle coat and it is not a proteid body.

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General physiological properties of diaphragm muscle.

By **FREDERIC S. LEE** and **A. E. GUENTHER**.

[From the Department of Physiology, Columbia University.]

Strips of the diaphragm of the cat, both curarized and non-curarized, have been excised after death and experimented with in moist chambers at room temperature. Their great resistance is demonstrated by the facts that they remain irritable two to three times longer than, and do several times the amount of work done by, a leg muscle, such as the extensor longus digitorum. Moreover, the diaphragm is not paralyzed by curare until long after the leg muscles have ceased to act. A most striking phenomenon is the tendency of the diaphragm strips to yield rhythmic twitches. This is much more pronounced than with the control leg muscles. It may be made manifest by the action of solutions of certain electrolytes, where the twitches are irregular in extent and duration; and by weak faradic currents, which insure more regular responses. With 40 to 100 faradic stimuli in the second, the twitches occur at a rate of from 2 to 4. They are much more marked in non-curarized muscle. When irregularities due to the stimulated current are excluded, the following factors may possibly interact in the production of the rhythmic responses: (1) There may be present the Wedenski effect; (2) the weak stimulus may affect from time to time different groups of fibers within the muscle, the irritability of the groups varying; (3) polarizing factors may be present. The relations of these and other possible factors are not yet established. A strip of diaphragm muscle as a whole has a decided power of rhythmical response, but it is not yet certain whether this power is possessed by the individual muscle fibers.

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The stimulation of nerve-endings in muscle and the theory of receptive substances.By **MARY WHITALL WORTHINGTON.**¹*[Physiological Laboratory of the Johns Hopkins University.]*

Langley has shown that the stimulating action of nicotine upon muscle is prevented by curare and that this antagonism is exhibited also in muscles in which the nerve fibers have been removed by degeneration. This and other facts have led him to formulate the hypothesis of special receptive substances present in the muscle upon which these drugs and other chemical stimuli exert their action, and furthermore he ventures the generalization, in contradiction of the usual belief, that "in no case do chemical substances have a special action on nerve-endings."

The series of experiments here reported were made at the suggestion of Dr. J. W. Warren to test the above hypothesis. The gastrocnemius muscle of the frog was used and its reactions were studied after immersion in solutions of sodium sulphocyanide and potassium sulphocyanide. The following results were obtained.

1. *Action of potassium sulphocyanide.*—This salt was used in hypertonic solutions (2 per cent. KCNS made up in a Ringer's mixture) and in isotonic solutions (1 per cent. KCNS in water). In both cases solutions of this salt caused an immediate rapid primary contraction followed by a prolonged contracture. This effect was not removed by the action of curare nor by the degeneration of the motor nerve fibers. It was obtained also by the action of other potassium salts, *e. g.*, potassium chloride—and must be considered as an instance of the "potassium contraction" described by other authors. The potassium ions may act upon the supposed receptive substance, but evidently their effect does not depend upon the presence of the nerve terminals.

2. *Action of sodium sulphocyanide.*—This salt was used also in hypertonic and isotonic solutions as in the case of the potassium sulphocyanide. In hypertonic (2 per cent.) solutions it caused a large primary contraction followed by a condition of contracture and by frequent isolated or grouped twitches of a coördinated or

¹ Deceased. Presented by W. H. Howell.

fibrillar character. In isotonic solutions the primary contraction was lacking, but fibrillar twitches occurred, although less frequently than in the hypertonic solutions. Hypertonic solutions (2 per cent.) of sodium chloride failed to give anything more than a small increase in tone. The marked primary contraction as well as the isolated twitches observed in the hypertonic solutions of sodium sulphocyanide were entirely lacking in the muscles of curarized frogs or in frogs in which nerve degeneration had been effected by cutting out a portion of the sciatic nerve. In the latter experiments observations were made upon frogs at varying intervals from 3 to 51 days after section of the nerve. It is noteworthy that the falling out of the contraction caused by the sodium sulphocyanide was observed as early as seven days after section and at a time when a response could still be obtained from the muscle by electrical stimulation of the peripheral end of the nerve. So, also, in the case of curare it was found that the sodium sulphocyanide contraction might be abolished even when the curarization of the animal was incomplete. Two per cent. solutions of sodium sulphocyanide have no stimulating action upon the sciatic nerve when immersed in the solution.

Conclusion.—The stimulating action of sodium sulphocyanide is not simply a sodium effect. The fact that its action is abolished by curare may be explained in accordance with Langley's hypothesis of receptive substances, but the fact that its action is readily removed by de-nervating the muscle is in contradiction to the generalization made by Langley in regard to the improbability of a special action of chemical substances upon the nerve endings in muscle.

Since hypertonic solutions of the sodium sulphocyanide do not stimulate the motor fibers in the sciatic nerve, their action in stimulating the muscle can be explained only on the assumption that they stimulate the nerve endings, if one bears in mind that this stimulating action falls out after the nerve fibers in the muscle begin to degenerate, as well as after administration of curare. It is noteworthy that the stimulating effect of this sodium sulphocyanide upon the nerve-terminals disappears in the incipient stages of the degeneration following section of the motor nerves.

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On the isolation of oöcytase, the fertilizing and cytolyzing substance in mammalian blood-sera. (Preliminary report.)

By **T. BRAILSFORD ROBERTSON.**

[From the Rudolph Spreckels Physiological Laboratory of the University of California.]

It has been observed by Loeb that the eggs of sea-urchins (*Strongylocentrotus purpuratus*) may be induced to form fertilization-membranes by immersing them in mammalian blood-sera which have been rendered isotonic with sea-water by the addition of NaCl. Occasionally, if the serum be especially potent, simple immersion of the eggs in the serum suffices to bring about this result, but as a rule previous treatment of the eggs with a sensitizing agent (SrCl_2 or CaCl_2) is required. Prolonged action of the serum upon sensitized eggs results in the cytolysis of the eggs. Very potent sera usually cause agglutination of the eggs as well, especially of sensitized eggs.

I have isolated from ox-serum a fraction which is extremely potent in fertilizing, cytolyzing, and agglutinating sea-urchin eggs.

To 860 c.c. of fresh, whipped, and centrifugalized ox-serum, which had been rendered isotonic with sea-water by the addition of $2\frac{1}{2}M$ NaCl solution, I added 400 c.c. of 7 per cent. BaCl_2 . A thick cloud was produced. This mixture after standing for an hour in a warm place until its temperature rose to 37°C . was centrifugalized. The entire precipitate, consisting of BaCO_3 , BaSO_4 , and the barium compound of the fertilizing agent and, possibly, of other substances, settled in the form of a cake at the bottom of the centrifuge-tubes. This precipitate was thoroughly drained and then suspended several times in 2 per cent. BaCl_2 and re-centrifuged in order to free it from adherent serum. It was then stirred up for an hour in 100 c.c. of $N/10$ HCl and the insoluble residue (probably barium sulphate) was centrifuged out. To the clear fluid thus obtained were added 10 c.c. of 10 per cent. Na_2SO_4 in order to free it from barium. This mixture was allowed to stand for some hours at 50° and then centrifuged. The clear

yellowish fluid thus obtained yielded no precipitate or opalescence upon the further addition of Na_2SO_4 and was therefore free from barium. To this fluid were added 4 volumes of acetone. A light flocculent precipitate was formed at once which settled readily. This was collected upon a hardened filter, washed in alcohol and ether, and dried for $3\frac{1}{2}$ days over H_2SO_4 at 36°C .

The substance thus obtained does not dissolve in sea-water. It dissolves readily in $N/10$ HCl and remains in solution upon neutralization. To this solution sufficient $2\frac{1}{2}M$ NaCl was added to render it isotonic with sea-water and the solution (0.5 per cent.) thus obtained was diluted to 1, $\frac{1}{2}$, . . . , etc., by the addition of sea water. On adding sea water, the mixture becomes very opalescent but the substance is not precipitated.

Eggs of *Strongylocentrotus purpuratus* which have not undergone previous sensitization are fertilized and agglutinated by solutions of this substance in dilutions of from 1 part in 200 to 1 part in 800. Eggs which have been sensitized by immersion for 4 minutes in $M/2$ CaCl_2 are fertilized and agglutinated by dilutions of from 1 part in 200 to 1 part in 1,600. Eggs which have been sensitized by immersion for 4 minutes in $M/2$ SrCl_2 are agglutinated by dilutions of from 1 part in 200 to 1 part in 25,000. The sensitizing action of SrCl_2 and CaCl_2 is clearly seen to reside in their power to precipitate the fertilizing agent upon the egg.

Since this substance is thermostable, withstanding 18 hours' exposure to a temperature of 50° without destruction, and there is some reason for suspecting that it is not present as such in circulating blood but is discharged from white corpuscles in shed blood, it would appear to present many analogies to the cytases or cell-liquefying substances found by Metchnikoff in white corpuscles. Accordingly, I propose that it be called "Oöcytase."

66 (675)

The food factor in hibernation. (Preliminary communication.)By **SUTHERLAND SIMPSON.**

[From the *Physiological Laboratory, Medical College, Cornell University, Ithaca, N. Y.*]

In those animals that hibernate the condition is generally believed to be brought about mainly by a low external temperature; when the winter cold sets in the animal retires to its burrow or nest and remains dormant until spring. Some, on the other hand, hold that a diminished food supply is the chief, or at any rate, an important cause of hibernation, and my experience with a colony of woodchucks (*Marmotta monax*) during the past winter would appear to support the latter view.

About the middle of September, 1911, eighteen woodchucks, which had been caught in box traps in the neighborhood of Ithaca, and were uninjured, were placed in eight artificial burrows about five feet below the surface of the ground, the object being to study, amongst other things, changes in the nervous system during hibernation. The burrows, which were packed with dry straw, opened into a central court into which food (clover, corn, apples, carrots, etc.) was placed every second day, and it was expected that when the animals began to hibernate the food would cease to be consumed.

In this locality I was told that woodchucks are rarely seen in the open fields later than the first or second week of October, and as the food still continued to disappear after that time, the burrows were opened up and the animals caught and examined to find out their condition, on the following dates.—Oct. 13, Nov. 11 and 27, Dec. 18 and 26. They were found to be quite active on all these occasions, with rectal temperatures somewhere in the neighborhood of 100° F.

The weather up till the end of December had been unusually mild for this climate, and this might possibly have had some influence in maintaining the wakeful condition, but from the beginning of January till the end of March the winter was excessively cold, the air temperature being often below zero fahrenheit,

and on two occasions 16° below. Notwithstanding this low temperature the food was still eaten by the woodchucks.

No food was supplied from Jan. 20 till Feb. 14 when the animals were again examined in the burrows. On that day their tracks in the snow were abundant. Six were found to be in a semitorpid condition, but they did not show the deep narcosis of true hibernation; the others were very active and combative, one having a rectal temperature of 99° F. Although no food had been placed in the inclosure for three weeks, it is still possible that they had some stored in their burrows, or that they ate the straw.

The six which showed some degree of torpor were removed to the laboratory, kept overnight outside the building in a large box amongst straw, and the next day, under ether anesthesia, a small lesion was made in the spinal cord of each. On the day following they were completely awake and active, and remained so until killed at various intervals after the operation. Food was supplied to these as well as to those left behind in the burrows from Feb. 14 onwards; they were inspected at short intervals from that date till the end of March and never showed any tendency to hibernate. The rectal temperature ranged from about 95° F. to 101° F.

These animals were not artificially protected from the weather in any way; the only circumstance in which their condition differed from that of their fellows in the open fields was that food was furnished them. The behavior of this colony would seem to point to the fact, therefore, that the absence of food supply is an important factor in determining the onset of hibernation.

67 (676)

A rapid method of producing a hemolytic serum.

By **FREDERICK P. GAY** and **J. G. FITZGERALD.**

[*From the Department of Pathology and Bacteriology, University of California.*]

Fornet and Müller¹ were first to suggest the intensive method of immunizing animals by giving large doses of serum for pro-

¹ Fornet and Müller, *Zeitschrift für biologische Technik und Methodik*, Strassburg, 1908, vol. 1, p. 201.

ducing precipitins intra-peritoneally on successive days. Such a method apparently gave rise to a potent precipitating serum and they claim equally successful results in producing hemolysins. These results as regards hemolysins were not confirmed in a later communication by Bonhoff and Tsuzuki.¹

We have found that one can obtain uniformly a sufficiently potent hemolytic serum for fixation tests by immunizing rabbits with washed sheep blood in a dose of one to two cubic centimeters administered intravenously on three successive days. The hemolytic titer of such a serum *four days after the third injection* is usually 1 to 2,000. In other words, it is possible to produce a thoroughly reliable hemolytic serum in one week by this method.

Further details of this intensive method of immunizing to produce hemolytic sera and also its use in producing precipitins, bacteriolysins, agglutinins, and antitoxins will form the basis of a more extensive communication to be published in the Pathological series of the University of California Publications.

68 (677)

Note on the effect of the internal secretions upon the secretion of epinephrin.

By ISAAC OTT and JOHN C. SCOTT.

One² of us was the first to show that the adrenal secretion relaxed and inhibited the rhythmic contractions of the intestine. Hoskins has shown that a dilution of 1-400 millions of epinephrin inhibits the rhythmic contractions. It thus becomes the most sensitive test for the presence of epinephrin. We tested its presence by the Magnus method. We injected a few grains of the filtered solution of the different glands into the jugular of the narcotized cat, and drew off, as Cannon has done, some blood from the vena cava above the openings of the adrenal veins, and defibrinated it. Normal blood defibrinated was then applied to a segment of the intestine of a narcotized rabbit and its rhythmic movements recorded. Then the blood, after the injection of the glandular filtrate, was applied to the same intestine and its move-

¹ Bonhoff and Tsuzuki, *Zeitschrift für Immunitätsforschung.*, IV, page 180.

² *Medical Bulletin*, 1897, p. 376.

ments registered. It was found that the injection of iodothyrim, parathyroid, infundibulin, thymus and pineal caused a distinct fall in tonus and inhibition of rhythmic contractions, showing the presence of epinephrin beyond normal in the blood. Normal blood of the cat never produces this effect, but stimulates tonus and rhythmic contraction. We have been careful to exclude albumen in these glandular tests, as the foreign albumen in the antithyroid serum of Möbius and in the diphtheritic antitoxic serum in 2 drop doses increases the amount of epinephrin in the blood. As cholin also produces an epinephrin reaction we can only be certain that iodothyrim and infundibulin stimulate the adrenals.

69 (678)

Standardization of the Wassermann reaction. Attempts to prepare a standard antigen and antibody.

By **J. G. FITZGERALD** and **J. B. LEATHES**.

[From the Department of Pathological Chemistry, Univ. of Toronto, and Department of Pathology and Bacteriology, Univ. of California.]

For some time past we have endeavored to determine more exactly the nature of the Wassermann reaction. This led us first to an investigation of the antigen. In this connection Noguchi, and we ourselves, have shown the importance of the substances contained in the acetone precipitate. Incidentally, we have found that an antigen containing these substances (lipoids) is available for use after a period of two years. The exact steps in the production of this antigen differ in certain details from methods heretofore published. The method will appear, shortly, elsewhere. The next step in the work was an effort to produce an antibody to this relatively stable antigen. Three attempts have been made and all were unsuccessful. No evidence of antibody formation could be shown by means of the reaction of fixation or the precipitin reaction. *These lipoid substances were found not to act as antigens.*

Had the production of an antibody been possible, the standardization of the Wassermann reaction could have been accomplished. This was the ultimate object of the work. No method

has been devised that permits of the "lipotropic" content of syphilitic sera being determined by quantitative methods by comparing them with such a standard serum as we have tried unsuccessfully to produce. Noguchi has shown that one can determine the absolute amount of a given syphilitic serum that will give complete fixation with a fixed amount of antigen, under certain conditions, at any given time.

In addition, for purposes of comparison at different times it would be necessary to have a standard antigen and a standard antibody (a "synthetic syphilitic" serum) both of relatively constant potency. These things are at present impossible. Quantitative standardization of the Wassermann reaction is, therefore, not feasible in the present state of our knowledge.

SCIENTIFIC PROCEEDINGS.

ABSTRACTS OF THE COMMUNICATIONS.

Forty-ninth meeting.

University and Bellevue Hospital Medical College. May 15, 1912.
President Ewing in the chair.

70 (679)

The effect of chemicals on the division rate of protozoa.

By **GARY N. CALKINS.**

[*From the Department of Zoölogy, Columbia University.*]

These experiments have been carried out during the past year for the purpose of finding out whether the products of nucleoproteid breakdown have any effect upon the division rate of free-living cells, the ultimate aim being to get some light on the controlling factors of cell division.

Two ciliated protozoa were used. One, *Actinobolus radians* Stein, lives exclusively on a diet of *Halteria grandinella*, another ciliate. The other, *Blepharisma undulans* Stein, lives on bacteria. Four control lines of each have been watched, fed, and the number of divisions recorded daily, and curves based upon the averaged division rates for five day periods, give the fluctuations in vitality of the organisms as measured by the division rates. Periods of depression, and of decreasing and increasing vitality have been clearly marked. Individuals for experimentation were in all cases sister cells of the control lines of the same dates.

The chemicals used included various amino acids, nucleins, and their derivatives, for many of which I am indebted to Dr. Levene and Dr. Walter Jones. In each experiment four strengths of chemical were used after empirical determination of the lethal dose. The number of divisions of all four lines were averaged

for five-day periods for comparison with the controls of the same periods, and all experiments were continued for at least ten days.

The results show that amino acids and their derivatives have but slight effect on the division rate at any period of vitality. The purins and their derivatives have but a slight effect on the division rate when vitality is very low or very high, but a marked effect of increasing the rate when vitality is decreasing (allantoin) or increasing (hypoxanthin, xanthin).

71 (680)

The first onflow and diastolic waves in the venous pulse.

By **E. M. EWING.**

[From the Department of Physiology of the University and Bellevue Hospital Medical College.]

Simultaneous records of the contractions of the auricle and ventricle, intraventricular pressure, arterial pulse, and the pulse of the superior vena cava were made.

Previous investigators have not agreed as to the time relations of the 3d positive (Mackenzie's "v") wave, some placing its appearance during ventricular systole, and others believing that it occurs in diastole. This confusion has arisen from the fact that Mackenzie's "v" wave in reality consists of two positive waves which are separate both in time and origin. (Bard described two such waves, but was not definite concerning the time relations.)

The first of these waves has been called the "onflow" wave, and the second, the "diastolic" wave. They are preceded, of course, by the auricular and systolic ("c") waves.

In a series of some fifty dogs, the onflow wave has always appeared just at the end of auricular relaxation, and therefore, during the first half of ventricular systole. The wave is terminated at the very beginning of ventricular diastole. The origin of the wave cannot be ascribed to the passive auricle, nor to the ventricle, the base of which is still moving downward, and which would tend, therefore, to produce a negative, rather than a positive wave. The wave must simply represent the increased pressure

resulting from the onflowing blood, which can now no longer enter the completely relaxed auricle, and must necessarily "back up" into the great veins. The instant ventricular relaxation commences, the base of the ventricle pushes up against the column of blood in the auricle and veins, and thus produces a still greater pressure—*i. e.*, the diastolic rise. In all of the experiments this diastolic rise has occurred synchronous with the beginning of ventricular relaxation, *before* the closure of the semilunar valves. The auricle, of course, is still passive.

The diastolic rise continues until the ventricle has relaxed sufficiently to allow the a-v valves to open, when the increased pressure in the auricle is terminated by the rapid outrush of blood. The resulting diastolic fall then continues until the end of ventricular relaxation, or, in other words, until the ventricle ceases to enlarge and receive the onflowing blood. The blood which cannot enter the ventricle, "backs up" into the auricle and veins, and thus produces the 2d onflow wave (Hirschfelder's "h"), in a manner similar to that in which the 1st onflow wave was originated.

The reason for the non-appearance of the 1st onflow wave in many jugular pulse tracings is that it is partially or completely fused with the diastolic wave. (The point of separation is indicated by a notch in many of Mackenzie's records.) The "a," "s," and "d" waves are essentially impact waves, and therefore travel faster than the onflow wave, which is dependent, for its rate of propagation, upon the rapidity of the onflow of blood from the periphery. The onflow wave appears just after the "s" wave in the lower part of the sup. vena cava, but by the time the effect of the "backing up" of blood has been felt in the veins of the neck, the onflow wave has been overtaken and obscured by the "d" wave.

The above conclusion is supported by figures from several experiments, showing that the onflow wave appeared in the jugular vein .05 second later than in the vena cava. The relative positions of the "a," "s," and "d" waves do not vary in the different regions.

72 (681)

On the action of the infundibular portion of the hypophysis upon vasodilators.

By J. AUER and S. J. MELTZER.

[From the Department of Physiology and Pharmacology of the Rockefeller Institute.]

By the investigations of Oliver and Schäfer, Howell and others, it has been established that by intravenous injections of an extract of the infundibular portion of the hypophysis a rise of blood pressure is produced, which, however is usually not as strong as the one produced by an injection of adrenalin. It is now generally assumed that, like adrenalin, the rise is produced by a stimulation of the constricting mechanism. On the basis of the hypothesis, that the hypophysis may raise the blood pressure not by a stimulation of the constricting, but by a *depression of the vasodilating mechanism*, we studied the effect of stimulation of the depressor nerve in rabbits soon after an intravenous injection of an extract of the hypophysis. We used for this purpose the pituitrin of Parke, Davis & Co., which is made up from the infundibular portion of the hypophysis. In some of the experiments the pituitrin was heated for the purpose of driving off the chloretone. In some of the experiments both vagi were cut to eliminate the inhibitory action through these nerves.

We may state briefly that in every experiment the irritability of the depressor nerve was either abolished or considerably reduced for a few minutes after the injection of the pituitrin. This was definite even before the rise which follows the injection began to develop and also during an insignificant rise. The larger the injected dose of pituitrin, the longer did the reduction of the irritability of the depressor nerve last. In 12 or 16 minutes, however, the irritability, as a rule, returned to normal. On repeating the injections, the reducing effect upon the irritability of the depressor became less and less pronounced.

We may recall here the fact, observed by Oliver and Schäfer and others, that during the rise of blood pressure from adrenalin, stimulation of the depressor nerve is ineffective. But this applies

only to the strong rise which sets in, as is known, immediately after injection of that substance. With the onset of the descent of pressure the depressor action of the depressor nerve becomes more and more effective. Here the inefficiency of the stimulation of the depressor may be due merely to the inability of the depressor nerve to overcome the high pressure. It is different, however, with the action of the hypophysis. Here the rise of blood pressure develops as a rule, gradually and sometimes it is even preceded by a fall. Furthermore in some instances the rise is comparatively insignificant. Nevertheless in all these conditions there is definite evidence of a striking reduction of the irritability of the depressor. We are therefore, for the present, inclined to look upon the discovered reduction of the irritability of the depressor nerve as a confirmation of our hypothesis that the infundibular portion of the hypophysis reduces the irritability of vasodilators. We may mention that studies upon the vasomotor effects of stimulations of the central end of the vagus nerve in dogs, which we shall not discuss here in detail, seem to furnish a further confirmation of this view. As to the locality where the hypophysis develops its action, whether upon the central or peripheral mechanisms or upon both, we shall not discuss at present.

73 (682)

On the reduction of toxicity of strychnin by the simultaneous administration of large quantities of fluid.

By **I. S. KLEINER** and **S. J. MELTZER**.

[From the Department of Physiology and Pharmacology of the Rockefeller Institute for Medical Research.]

In the course of some experiments on adrenalin glycosuria in which the simultaneous injection of blood, serum or lymph with adrenalin was studied, it became manifest that the significance of the factor of dilution had to be previously established. It was thought that the study of the effect of dilution upon strychnin poisoning would throw some light upon this. The definite and instructive results which were obtained will be stated here very briefly.

Controls.—Six rabbits received subcutaneously 0.45 mg. strychnin per kilogram body weight. All six had convulsions, with fatal termination in three. Nine animals received 0.5 mg. per kilo; all had convulsions, terminating fatally in four. In 15 controls, then, a dose of 0.5 mg. strychnin or less per kilo body weight brought on convulsions in every one and a fatal termination in 7; in other words 0.5 mg. strychnin proved to be toxic in 100 per cent. and fatal in 47 per cent.

Strychnin diluted in 100 c.c. of normal saline.—Ten rabbits received subcutaneously doses of strychnin varying between 0.7 and 0.84 mg. per kilo body weight diluted in 100 c.c. of 0.9 per cent. sodium chlorid. Of these only two had convulsions, one of which died. In other words, strychnin in great dilution is considerably less toxic; doses which exceed the minimal fatal dose proved to be toxic only in 20 per cent. and fatal in 10 per cent.

Strychnin and saline injected in separate places.—In a series of eleven rabbits each received subcutaneously 0.5 mg. strychnin per kilo body weight at one point shortly after having been injected with 100 c.c. of 0.9 per cent. sodium chlorid at another place. Of these only three had convulsions and only one died. In other words, when 100 c.c. of saline was injected in another part of the body, a dose of 0.5 mg. per kilo of body weight, which in controls proved toxic in 100 per cent. and fatal in 47 per cent., was toxic only in 27 per cent. and fatal in 9 per cent.

Strychnin subcutaneously and water given by mouth.—Eight rabbits received 0.5 mg. strychnin per kilo body weight subcutaneously shortly after 100 to 150 c.c. of water had been given by mouth. Of these animals only two had convulsions and none died, that is, in these cases 0.5 mg. strychnin proved to be toxic only in 25 per cent. and caused no fatalities. Twelve animals were given strychnin subcutaneously, in doses varying between 0.52 and 0.56 mg. per kilo body weight, receiving at the same time 100 c.c. of water by mouth. Of these animals four had convulsions and none died. In other words even doses which definitely exceed the sure toxic dose of 0.5 mg. per kilo, proved toxic only in 33 per cent. with no fatalities at all, when at the same time, a comparatively large quantity of water was given by mouth.

These experiments seem to demonstrate conclusively that the

toxicity of strychnin is definitely reduced not only when it is administered in great dilution, but also when saline or water is administered nearly simultaneously in other parts of the body, thus, perhaps, diluting the poison within the circulation. These results are of general theoretical interest and have obviously also a practical bearing, neither of which we shall discuss here.

74 (683)

The influence of the infundibular portion of the hypophysis upon the pupil.

By **S. J. MELTZER.**

[From the Department of Physiology and Pharmacology of the Rockefeller Institute.]

The action of the extract of the hypophysis is similar to that of adrenal extract in the first place by the influence which both exert upon blood pressure. There seems to be also some similarity in their action upon the uterus and intestines. With regard to the action of hypophysis upon the frog's pupil which, as is well known, becomes definitely dilated by adrenalin, opinions differ. While Cramer and others report a dilatation, Kepinow and Gottlieb recently stated that in their hands the extract of the hypophysis caused a constriction of the frog's pupil. In my own observations upon the enucleated bulbi from *Rana pipiens*, heated and unheated *pituitrin* (Parke Davis & Co., prepared from the infundibular portion of the hypophysis) *in most instances caused a dilatation of the pupil*. The extent of the dilatation varied greatly in various eyes and was never as striking as is observed under the influence of adrenalin. In a smaller number no dilatation of the pupils took place; *but in no instance have I observed a miosis following the bathing of the bulbi in pituitrin*.

A very striking test is the action of adrenalin on the pupil of mammals (rabbit or cats) on the side on which the superior cervical ganglion had been removed 24 hours or longer. If a sufficient dose was used, that pupil showed a maximal dilatation which may last for hours, while the pupil on the normal side remains unchanged. I have studied this test with *pituitrin*. In six rabbits

in whom one superior cervical ganglion had been removed, either on the right or on the left side, I have injected at various times various doses of pituitrin—1 c.c., 2 c.c. and 3 c.c.—through the marginal ear vein. *At no time did a dilatation of the pupil on the operated side follow these injections, neither soon nor late. Both pupils, however, and especially that of the eye on the operated side, showed a constriction of short duration immediately after the injection.*

Here we meet, then, with a definite difference between the action of adrenalin and pituitrin which, in some cases, might assist in the identification of the nature of the blood-raising principle found to be present in some fluids.

75 (684)

Observations on the relation of carbon dioxide and oxygen to the development of certain amphibian embryos.

By **A. M. BANTA.**

[*From the Station for Experimental Evolution, Cold Spring Harbor, Long Island, New York.*]

The following observations were made during the past two seasons upon material kept for other purposes.¹

Eggs of all the species mentioned below were placed when fresh or in early cleavage in artesian water containing 1.32 per cent. of CO₂, the amount normal to large open ponds here being only about 0.04 per cent.

Ambystoma punctatum.—Development was at the normal rate with no mortality of embryos traceable to the CO₂ in the water. The larvæ likewise lived fairly well, though in many cases not so well in the CO₂ water as in pond water.

Spelerpes bilineatus.—Cleavage and later development were probably at the normal rate, but there was a large mortality percentage in standing or running artesian water. The mortality was less in standing water from ponds but thoroughly oxygenated water comparatively free from CO₂ was necessary to get the highest percentage of developing embryos.

¹ Observations on *Spelerpes*, *Rana pipiens* (?), and *Rana sylvatica* were made on material kept in collaboration with Dr. R. A. Gortner, of this station.

Bufo lentiginosus.—Only a small percentage developed at all and none beyond early cleavage.

Hyla versicolor and *Hyla pickeringii*.—A few went through cleavage but none beyond.

Rana pipiens (?).—Mortality was very large during early stages but perhaps 5 per cent. developed until the embryos were considerably differentiated and about 3 mm. in length. None developed further. In two of the ponds observed all the eggs and embryos of this species died much as those placed in CO₂ water in the laboratory. These were ponds practically without aquatic plants and containing great quantities of decaying leaves and other plant debris and therefore doubtless had much CO₂ in the water.

Rana sylvatica.—The development was apparently at the normal rate. In many cases the larvæ hatched, but though active for a day or two and clinging to the jelly mass and sides of the jars in the usual fashion took no food and developed no further. All died within a few days. In other jars where considerable masses of the eggs were placed and where large numbers died before hatching the larvæ in the interior of the masses and thus least exposed to the CO₂ water survived longest.

Often the eggs of the inner portions of the egg masses of *Rana sylvatica* and *Ambystoma tigrinum* (all of which were otherwise developing normally) show a retarded development, progressively the more so the farther the eggs are from the periphery of the mass, due to insufficient oxygen. In one egg mass of *Ambystoma* the exterior embryos of the mass were 10.2 to 11 mm. long and almost ready to hatch, while at the other extreme those deepest within the mass were only 3.6 mm. long and still in the late neural groove stage. In most cases in the ponds where the *Ambystoma* eggs are laid, as well as in jars in the laboratory, a portion of the interior of the masses die before hatching. In one pond near the laboratory protected from wind and containing very quiet and poorly oxygenated water perhaps 90 to 95 per cent. of the eggs die each year. That insufficient oxygen is the cause was indicated by the low percentage mortality in a few masses left almost entirely exposed to the air by the lowering of the level of the pond. These conditions were imitated in the laboratory with the result

that in some cases 60 to 100 per cent. of the eggs of egg masses kept in a depth of 12 to 18 inches of quiet, poorly oxygenated water died, while in similar adjoining vessels eggs less than half submerged developed almost without exception.

76 (685)

Direct observation of cell division in mammalian tissue.

By **ROBERT A. LAMBERT.**

[From the Department of Pathology, College of Physicians and Surgeons, Columbia University.]

Connective tissue cells of the rat cultivated outside the body in rat plasma for as long as seventy-six days formed the material for observation. For maintaining activity for such a period, the pieces of tissue were transferred to fresh plasma at intervals of five to ten days. Measures employed by Carrel for rejuvenating the cells in old cultures were found to be unnecessary.

We have found that the process of karyokinetic division may be followed in the living cells. The earlier phases often escape notice. The later phases, however, may be observed with ease even with the lower powers of the microscope. In actively growing cultures the time required for the entire process is from forty to sixty minutes. The time elapsing between the divergence of the masses of daughter chromosomes to complete division of the cytoplasm averages about ten minutes. In slowly growing cultures the process may be retarded. A half hour to an hour after division is required for the daughter cells to develop the form and staining qualities of the resting cell. These time periods relate to observations made on cells at 35-37°C. At lower temperatures (25-30°) the process is slower.

Cells containing numerous fat droplets have been seen to divide as rapidly as cells free from fat.

Amitotic division has not been observed.

Cells after division have been followed and further division noted. The size reached by these daughter cells was approximately that of the parent cells. This observation affords proof that true growth takes place in cells cultivated in vitro.

77 (686)

The effect of drying upon the viability of bacteria.By **C. E. A. WINSLOW** and **F. ABRAMSON**.*[College of the City of New York.]*

The curve of viability, measuring the rate of decrease among bacteria exposed to an unfavorable environment, has been determined for many conditions. Drying is known to cause a rapid elimination, but no exact quantitative determinations have been made. In the experiments here reported, colon bacilli were used. One cubic centimeter of a 48-hour broth culture was mixed with $2\frac{1}{2}$ grams of sea sand spread out in an ordinary Petri dish. Duplicate dishes prepared in this way were covered with porous earthenware tops and kept for various periods of time from four hours to ten days. At the end of each period nine cubic centimeters of sterile water were added to the sand in one of the dishes and well mixed by careful agitation. Portions of this water were then plated in duplicate on agar in the usual manner.

The results of eight series of tests are shown in the table below expressed in percentages of the original number of bacteria present. The original numbers in different series varied from 4,150,000 to 117,300,000 per gram of sand, and the final number remaining after ten days in Series II and III were 20,700 and 18,900 per gram, respectively. The average temperature and humidity of the room in which the plates were kept is shown for the last five series at the bottom of the table.

PERCENTAGE OF ORIGINAL NUMBER SURVIVING.

Period. Hours.	Series.							
	I.	II.	III.	IV.	V.	VI.	VII.	VIII.
4						76.45		
5½						57.18		
6				75.90			79.82	
7					57.56	37.46		57.76
8				67.23	59.30		69.03	
10					44.48			41.38
24	.85	.85	.85					
48	.16	.16	.15					
120	.08	.06	.06					
166	.04	.04	.04					
216		.02	.02					
240		.02	.02					
Average temperature				69°	69°	70°	69°	69°
Average relative humidity . . .				90%	72%	60%	90%	72%

The results are quite concordant when the dryness of the atmosphere is taken into consideration. Series VI showed a more rapid reduction than the others during the first 7 hours and the relative humidity was 60 per cent. Then came Series V and VIII with a relative humidity of 72 per cent., while in Series IV and VII with an atmospheric humidity of 90 per cent., nearly 70 per cent. of the bacteria were alive after 8 hours.

The general rate of reduction was directly proportional to the time, during the first 24 hours, and then fell off more and more gradually. As a rule, intestinal bacteria in any foreign medium, colon bacilli in water, for example, decrease rapidly at first and more and more slowly as time goes on, following almost a parabolic curve. Most die at first, but a few persist for a long time. In its general relations the curve for drying is similar. 99 per cent. of the bacteria are gone after 24 hours while 2 out of 10,000 persist after 10 days. The curve for the first 24 hours is however here practically a straight line. 50 per cent. perished after 10 hours, and 99 per cent. after 24 hours. This is to be explained by the fact that during this period the bacteria were not exposed to constant conditions, since the originally moist sand was becoming progressively dryer. Determinations made by weighing at intervals duplicate samples prepared just like those which were inoculated with the bacteria showed that nine tenths of the moisture in the sand was gone after 10 hours and practically all of it was gone after 24 hours (with an atmospheric humidity of 80 per cent.). With a constant unfavorable environment, the reduction of bacteria proceeds at a decreasing rate. With an environment growing more and more unfavorable we might expect an approximately even rate of reduction such as is indicated here.

So far as the absolute reduction is concerned, it appears that drying is highly inimical to the bacteria studied. A uniform reduction of 99 per cent. is indicated after 24 hours. It takes over a week to reach such a point when colon bacilli and similar intestinal forms are stored in water.

Determination of the amino-acid nitrogen in the urine.By **S. R. BENEDICT** and **J. R. MURLIN.***[From the Cornell University Medical College.]*

Since the abandonment of the Pfaundler method for determination of the amino-acid nitrogen of the urine, the only direct methods proposed which have met with any favor, are the gasometric method of D. D. Van Slyke and the titration method of Henriques and Sørensen. In our hands the Van Slyke method as originally described¹ has not proved entirely satisfactory, (1) because of the difficulty of removing all the ammonia after conversion of urea, and (2) because poly-peptids and other condensation products of amino-acids, *e. g.*, hippuric acid, are estimated as well as free amino-acid nitrogen. The method, therefore, probably gives results which are too high.

The Henriques and Sørensen method as improved by the authors themselves² likewise presents some difficulties. For example, as objected by de Jager and since admitted by Henriques and Sørensen, in the presence of large quantities of ammonia the total titration is less than the sum of the ammonia N and amino-acid N done separately. It is therefore necessary first to remove the ammonia. Henriques and Sørensen recommend for this the method of Krieger and Reich slightly modified. This is essentially the method well known in this country by Shaffer's name. Since the method is based on distillation under diminished pressure, it is not adapted to rapid determinations in a series of urines simultaneously. Besides, as used by Henriques and Sørensen, we have not been able to obtain as high ammonia figures as by the Folin method. Use of the latter method for removal of ammonia, while perfectly satisfactory for small samples of urine (10 or 20 c.c.) is not satisfactory for a sample large enough to give a titration for amino-acid nitrogen (40–50 c.c.).

Another objection to the Henriques and Sørensen procedure is the difficulty of titration with phenolphthalein in a barium filtrate because of interference of carbon dioxide.

¹ PROC. SOC. EXP. BIOL. AND MED., 1910, VII, p. 47.

² *Zeitschr. f. physiol. Chemie*, 1909, LXIV, p. 120.

These various difficulties have led us to return to the precipitation of ammonia by means of phosphotungstic acid. Gumlich¹ showed originally that the proper conditions for removal of ammonia by 10 per cent. phosphotungstic acid are a strongly acid urine and sedimentation for 24 hours. We have satisfied ourselves that this strength of phosphotungstic acid does not precipitate the mono-amino acids in the concentration usually found in urines. Instead, however, of removing the urea from the phosphotungstic filtrate and the determination of amino-acid nitrogen by difference, as in the original Schöndorff-Pfaundler method, or the modifications of it by Krieger and Schmidt, Van Leersum, and others, we remove the phosphotungstic acid by means of tribasic lead acetate and litharge, and titrate for mono-amino acids in the filtrate (after removal of lead) according to the procedure of Henriques and Sørensen. The filtrate is water-clear and free of any constituents which can interfere with the formalin titration.

COMPARISON OF THE HENRIQUES AND SÖRENSEN METHOD WITH MODIFIED METHOD.

Urine	No.	H. and S.	Modified Method.
Case 1. Pernicious vomiting.	Urine No. 1	0.215 gm. NH_2N	0.015 gm. NH_2N
	Urine No. 2	0.434 gm. NH_2N	0.048 gm. NH_2N
	Urine No. 4	0.268 gm. NH_2N	0.025 gm. NH_2N
	Urine No. —	0.245 gm. NH_2N	0.023 gm. NH_2N
Case 2. Eclampsia.	Urine No. 3	0.397 gm. NH_2N	0.120 gm. NH_2N
	Urine No. 7	0.157 gm. NH_2N	0.035 gm. NH_2N
	Urine No. 8	0.375 gm. NH_2N	0.148 gm. NH_2N
	Urine No. 11	0.210 gm. NH_2N	0.155 gm. NH_2N

All the urines contained a large amount of ammonia. It would seem from this comparison that the Henriques and Sørensen method like the Van Slyke method gives results (especially on pathological urines) even after the supposed removal of ammonia which may be quite misleading.

The following are a few of the results obtained with pure substances.

A. Pure Solutions:

1. 20 c.c. *N*/20 leucine, purity tested by Kjeldahl and formol titration, added to 5 c.c. *N*/10 NH_4Cl < 200 c.c.; 45 c.c. of final filtrate, titration 2.4, theory 2.28.

¹ *Zeitschr. f. physiol. Chemie*, 1893, XVII, p. 13.

2. 20 c.c. leucine + NH_4Cl < 180 c.c.; 50 c.c. final filtrate, titration 2.7, theory 2.77.
3. Mixture of urea, $(\text{NH}_4)_2\text{SO}_4$, uric acid, alanin, glycocoll, glutamic acid (all tested substances), containing 0.144 gm. amino-acid nitrogen, yielded by new method 0.132, 0.148, 0.143 gm.

B. Pure Substances added to urines.

1. 200 c.c. normal urine; 100 c.c. final filtrate, titration 9.6 c.c. $N/10$ NaOH.
200 c.c. normal urine + 20 c.c. $N/20$ leucin; 100 c.c. filtrate, titration 11.8 NaOH
Difference 2.2 c.c., theory 2.5 c.c.
2. 200 c.c. urine of puerperient woman; 100 c.c. filtrate, titration 9.7 $N/10$ NaOH.
200 c.c. urine of puerperient woman + 20 c.c. $N/10$ alanin, titration 14.7 $N/10$ NaOH.
Difference 5.0 c.c. $N/10$ NaOH, theory 5.0 c.c.

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Picrolonates of the monoamino acids.¹

By **P. A. LEVENE** and **DONALD D. VAN SLYKE**.

[*From the Rockefeller Institute for Medical Research, New York.*]

Picrolonic acid, used by Steudel to precipitate the hexone bases, and later shown by Mayeda to form salts with the aromatic amino acids tryptophane and phenylalanine, also forms crystalline salts of normal composition with the other monoamino acids obtained on hydrolysis of proteins. The salts are made by dissolving molecular proportions of amino acid and picrolonic acid in a minimum amount of boiling water. The picrolonates crystallize from the cooling solutions, usually while they are still warm. In cold water many of them are very insoluble. In alcohol they are all more soluble than in water. Following is a list of the amino acids of

¹ After this title had been sent to the secretary an article by Abderhalden and Weil appeared describing picrolonates of glycocoll; d-alanine, and dl-leucine (*Ztschr. physiol. Chem.*, 78, 150). They were formed in alcoholic solution, which yielded products of abnormal composition in the cases of glycocoll and alanine.

which picrolonates were prepared, after each being given the solubility of the picrolonate in grams per 100 c.c. of water at 20°-23°, and the melting point. The picrolonates are arranged in order of solubility. *Dl-phenyl-alanine*, 0.12, 212° (decomp.); *Tyrosine*, 0.29, blackens at 260°; *l-phenyl-alanine*, 0.34, 208°; *dl-leucine*, 0.53, indefinite above 140°; *l-leucine*, 0.55, indefinite at about 150°; *d-isoleucine*, 0.58, 170°; *dl-valine*, 0.81, indefinite above 150°; *dl-serine*, 0.98, decomposed 265°; *glycocoll*, 0.99, 214°; *dl-alanine*, 1.01, 216°; *d-valine*, 1.20, 180°; *d-alanine*, 1.61, 214°; *dl-aspartic acid*, 1.69, blackens at 130°; *dl-glutaminic acid*, 2.37, 194°.

Nearly all the picrolonates decompose more or less on melting, and the melting points are not sharp. L-Phenyl-alanine picrolonate is much more soluble in alcohol than the racemic salt, and can be separated from most of the racemic substance by solution in alcohol. The optically active compound has a sp. rotation in absolute alcohol of + 30°. The specific rotation of d-isoleucine picrolonate in alcohol is + 33.3°. Phenyl-alanine can be separated from glutaminic or aspartic acid by dissolving the mixture with enough picrolonic acid to combine with the phenyl-alanine only. The picrolonate of the latter crystallizes pure. It is probable that other amino acids can be separated by similar use of picrolonic acid. The pyrrolidine acids, proline and oxyproline, do not readily yield picrolonates when treated as described above.

80 (689)

An improved apparatus for gasometric determination of amino nitrogen.

By **DONALD D. VAN SLYKE.**

[From the Rockefeller Institute for Medical Research, New York.]

The apparatus differs from that reported at the meeting of this society in December, 1909, in that: (1) The desamidizing bottle with stopper holding the 10 c.c. burette and tubes is replaced by a bulb into which the tubes and burette are sealed; (2) the Hempel absorption pipette is modified so that it can be suspended from hooks; (3) both absorption pipette and desamidizing bulb are so arranged that they can be shaken by a motor. The apparatus,

without losing any of the accuracy of the original, is much more convenient because it can be used an indefinite number of times without disconnecting the parts, and the shaking by hand is replaced by the less laborious and more efficient motor. The latter also increases the rapidity, so that with one apparatus a determination can be made every seven or eight minutes.

81 (690)

The nature of the free amino groups in the native proteins.

By **DONALD D. VAN SLYKE** and **F. J. BIRCHARD**.

[From the Rockefeller Institute for Medical Research, New York.]

The fact that at least some proteins contain a small but definite proportion of their nitrogen in the form of free amino groups capable of reacting with nitrous acid has been proven by one of us. Levites and Skraup failed to obtain lysine from proteins which had been treated with nitrous acid before hydrolysis. This indicates that the ω -NH₂ group of lysine, $\text{NH}_2 \cdot (\text{CH}_2)_4 \cdot \text{CH}_2(\text{NH}_2) \cdot \text{COOH}$, may be free in the protein molecule. As lysine is peculiar among the amino acids in possessing an ω -NH₂ group, it appeared possible that this might be responsible for all or most of the amino nitrogen determined. We have, therefore, determined the free amino nitrogen in ten proteins in which the lysine has already been quantitatively determined in either our laboratory or in Osborne's.

Protein.	Per Cent. of Total N in Lysine.	$\frac{1}{2}$ Lysine N.	Free Amino N.
Ox-hemoglobin.....	12.0 (Van Slyke)	6.0	5.6
Fibrin.....	11.4 (Van Slyke)	5.7	5.3
Hemocyanin.....	8.5 (Van Slyke)	4.25	4.3
Casein.....	6.9 (Osborne)	3.45	3.4
Gelatin.....	6.3 (Van Slyke)	3.15	3.1
Egg albumin.....	4.0 (Osborne)	2.0	2.4
Edestin.....	3.8 (Van Slyke)	1.9	1.2
Zein.....	0.0 (Osborne)	0.0	0.3

Albumoses from Witte Pepton.

Heteroalbumose.....	10.3	5.15	6.3
Protoalbumose.....	9.6	4.8	6.6

Without exception the free amino N of the native proteins

equals within a fraction of a per cent. that of the ω -group of the lysine. It appears that the ω -group of lysine constitutes practically all of the free amino nitrogen of the native proteins determinable with nitrous acid. The albumoses show appreciably more free amino nitrogen, which is to be expected from the fact that the protein molecule is partially broken down in their preparation.

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An experimental study of anti-anaphylaxis.

By **R. WEIL** and **A. F. COCA.**

[From the Laboratories of Experimental Therapeutics and Experimental Pathology, Cornell University Medical School, New York City.]

If a guinea-pig be given a single injection of a foreign proteid, it becomes, after the lapse of 10 to 14 days, actively sensitized to that proteid, in such wise that the reinjection of the same, in doses far too small to cause any symptoms in a normal animal, produces almost immediate death with convulsions. If, however, such a sensitized pig, after the sensitizing injection, be given a second dose, too small to induce its death, it immediately passes into a condition of anti-anaphylaxis, in which it is refractory to the foreign proteid in question, and may manifest no symptoms even after the injection of doses toxic to normal animals. This refractory stage lasts for weeks or months. In the same way, an animal may be passively sensitized by the introduction into its veins or peritoneum of the serum of another animal, which has been previously immunized or sensitized to a foreign proteid; in this case, too, the injection of a relatively small, *i. e.*, sublethal, dose of the same proteid into the passively sensitized animal produces a condition of anti-anaphylaxis.

By no experimental device hitherto employed has it been possible to alter this condition of anti-anaphylaxis. The theories offered to explain it are numerous. Friedemann, in his general review of anaphylaxis, in 1911, cites three hypotheses, those of Gay and Southard, of Besredka, and of Friedberger, all of which he proves to be untenable, and offers three other possible explana-

tions. He concludes that anti-anaphylaxis presents a "most interesting, novel, and as yet unexplained phenomenon."

The following experiments appear to us to throw much light on the problem. Guinea-pigs have been actively sensitized, by injection, to a foreign proteid; after the lapse of about two weeks, they have been rendered anti-anaphylactic by the intra-peritoneal injection of a sublethal dose of this proteid. (That anti-anaphylaxis had actually been so induced was demonstrated by the injection of relatively enormous doses of the proteid into controls similarly treated, without toxic effect.) The anti-anaphylactic animals have then been *re-sensitized*. This re-sensitization is accomplished by bleeding to death another guinea-pig, sensitized to the identical proteid, and then injecting his serum, in amounts of from 2 to 5½ c.c., into the veins of the anti-anaphylactic animal. After the lapse of less than 24 hours, the re-sensitized pig has been tested by an intravenous injection of the foreign proteid. In each and every case, the pig, upon undergoing this test, has manifested the typical symptoms of anaphylaxis, with immediate death. In other words, such a pig acts exactly like a normal pig, which has been passively sensitized by the introduction of serum from an anaphylactic pig.

If instead of a sensitized pig, one makes use of the serum from a pig highly immunized by means of repeated injections, re-sensitization of the anti-anaphylactic animal is accomplished in the same manner.

If an actively anti-anaphylactic pig be passively re-sensitized with the serum of a rabbit immunized to the same foreign proteid, he too becomes hypersensitive, and is killed by a subsequent dose of this proteid.

The same experiments can be performed in the case of animals rendered anti-anaphylactic after passive sensitization. If, during the refractory period, say two days after the anti-anaphylactizing dose, they are re-sensitized to the same foreign proteid by the reintroduction of an immunized rabbit's serum, they may be killed in the typical manner by the re-injection of the proteid. The only difference between passive anaphylaxis as primarily and as secondarily induced, is that in the latter somewhat larger doses are required to re-sensitize. The cause of this difference is being investigated and will form the subject of a later report.

These experiments in anti-anaphylaxis were originally performed with horse serum. In order to avoid any possible source of error, however, due to the complex character of this material they were repeated with a solution of crystalline egg albumen which had been four times re-crystallized, and the same results were obtained.

It appears from these experiments that anti-anaphylaxis is a condition in which an animal becomes refractory to the toxic effects of a foreign proteid simply through the exhaustion from his blood of those bodies which induce the reaction. The proof hereof lies in the fact that the simple re-introduction of these bodies with the blood of another sensitized animal restores him at once to his original condition of anaphylaxis. The bodies which induce the reaction are, so far as we know, two: first, the "anaphylactic anti-bodies," which resemble in character, and may be identical with, the amboceptors; second, the complement substances of the blood.

It is unlikely that the complement is the substance herein at fault, inasmuch as Friedemann states, as the complement is rapidly restored to its normal amount in anti-anaphylactic pigs, whereas the condition of anti-anaphylaxis persists. We have tested whether the complement plays an important rôle by two sets of experiments. In the first place, the animals have been simultaneously sensitized by hypodermic injection to two different forms of foreign proteid, namely horse serum and egg albumen. They have then been rendered anti-anaphylactic to one of these. Immediately, thereafter, it has been found that their sensitiveness to the other albumen is little, if at all, impaired. This indicates that the complement cannot be deficient. In the second type of experiments, the pigs, having been made anti-anaphylactic to egg albumen, have been given an intra-venous injection of 5 c.c. of normal guinea-pig serum, which would, of course, suffice to supply any defect of complement. When now re-injected with egg albumen, they fail to evidence any sensitiveness. This indicates, therefore, that something other than complement, necessary to the anaphylactic reaction, has been removed from the blood in anti-anaphylaxis. It seems to us, therefore, that animals are anti-anaphylactic simply through the absence of the appropriate

anti-bodies from the serum. If these are supplied, an animal passes directly into the anaphylactic condition again, and this reversal could conceivably be repeatedly renewed.

CONCLUSIONS.

1. Guinea-pigs which have been rendered actively anaphylactic by a preliminary injection of foreign proteid (horse serum, egg albumen), and have then been made anti-anaphylactic by the injection of a sub-lethal dose of this proteid, may be immediately re-sensitized by the introduction of serum from a pig sensitized, or one immunized to the same proteid. Death is then produced, with typical anaphylactic symptoms by the intravenous injection of an amount of this proteid which to normal pigs is non-toxic.

2. Actively anti-anaphylactic pigs may be re-sensitized with serum derived from a rabbit immunized against the same proteid.

3. Passively sensitized pigs, rendered anti-anaphylactic by the usual methods, can be re-sensitized by the re-introduction of an immune serum.

4. A pig simultaneously sensitized to two different foreign proteids, may be rendered anti-anaphylactic to one of these by the usual methods, while its sensitiveness to the other remains unimpaired. This demonstrates that anti-anaphylaxis cannot be due to exhaustion of complement, since complement is amply present.

5. The introduction of normal guinea-pig's serum into an anti-anaphylactic animal fails to re-sensitize. Some factor other than complement, therefore, must be introduced in re-sensitization.

6. The absence of available anaphylactic antibodies appears to be the cause of the refractory condition known as anti-anaphylaxis, and re-sensitization is due to their re-introduction.

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The toxicity of foreign leucocytes.

By **WILFRED H. MANWARING.**

[From the Rockefeller Institute for Medical Research.]

The injection of from 0.7 c.c. to 1.0 c.c. of rabbit leucocytes into the cerebral meninges of dogs is apparently invariably fatal.

The animals show no immediate symptoms; but about two hours later there is beginning incoördination, rigidity and respiratory distress, increasing to collapse about the fourth hour, and death about the sixth. An occasional dog survives till the twenty-fourth hour. Autopsy usually shows extensive local hemorrhagic, inflammatory and necrotic changes.

Horse leucocytes similarly injected produce symptoms of the same general nature, though less severe. About two thirds of the dogs injected with horse leucocytes recover. A reinjection of these dogs, however, or the injection of dogs whose meninges have been previously injured by tubercle bacilli, is almost invariably fatal.

The injection of 0.5 c.c. of rabbit leucocytes into the spinal meninges of monkeys produces slight symptoms from which most of the monkeys recover. Larger amounts are usually fatal.

Horse leucocytes are less toxic for monkeys, producing few if any symptoms, even when injected in 1.0 c.c. doses. The toxicity of both leucocytes however increases on repeated injection, the third injection often being fatal. Autopsy in such cases often shows edema of the lungs as the apparent immediate cause of death.

These tests have a bearing on the possible therapeutic uses of leucocytes in meningeal infections.

84 (693)

The occurrence, and the significance, of tyrosinase in the reproductive organs of certain amphibians.

By **ROSS AIKEN GORTNER.**

[From the Laboratory of Biological Chemistry of the Station for Experimental Evolution, The Carnegie Institution of Washington.]

Tyrosinase—the enzyme which oxidizes tyrosin to produce a black, insoluble, pigment-like compound—has been shown by Phisalix (*C. R. Soc. Biol.*, 50, p. 793, 1898) to occur in the skin of the European frog, *Rana esculenta*. Gessard, later (*ibid.*, 56, p. 285, 1904), shows that the same enzyme occurs in the skin of the toad, *Bufo vulgaris*, and in the frog, *Rana temporaria*. In discussing the

importance of the tyrosinase Phisalix says: "It is probable that the oxidase presides over the oxidations within the organism . . . and plays the rôle of fixing oxygen in cutaneous respiration." If such is the case, and the production of the pigment in the skin is only a secondary reaction, or the elimination of a byproduct, the study of this enzyme becomes of much greater importance than merely as a pigment-producer.

In every instance where the mechanism of melanin formation has been elucidated, it has been found that pigmentation is due to the interaction of tyrosinase and a chromogen. It therefore seemed probable that the enzyme might be present in the ovaries of those amphibians which deposit pigmented eggs, and might be responsible for the pigment formation. I have found that tyrosinase is present in the ovaries of the green frog, *Rana clamata*, and the wood frog, *Rana sylvatica*. Owing to the greater ease in securing material of various ages most of the tests were carried out using material from the green frog. *In every instance the intensity, and the rapidity of the development of the tyrosinase test was in inverse proportion to the amount of pigment present in the eggs.* Ovaries which were immature, and contained no pigmented eggs, gave a positive tyrosinase test in a very few hours, partially pigmented ovaries required in some instances as much as 96 hours to produce a positive test, while the ovaries which contained ripe eggs failed to give any indication of the presence of the enzyme in 168 hours. All solutions were kept sterile by the addition of a few drops of chloroform. When partially pigmented ovaries were used the "blank" (no tyrosin added) usually showed considerable darkening, which, however, did not appear in a boiled check, showing that a chromogen was also present. It would, therefore, appear that the pigmentation of the eggs of the frog is due to an oxidation induced by tyrosinase, and that as the pigmentation progresses the amount of tyrosinase decreases, until there is no perceptible amount of the enzyme present in the unfertilized eggs which are fully ripe.

The tadpoles at the moment of liberation from the egg contain tyrosinase, as do also the larvæ of the salamander, *Ambystoma punctatum*. Inasmuch as the ripe unfertilized ova do not seem to contain tyrosinase, it seemed probable that the enzyme might be

added through the sperm, and on testing the testes of adult green frogs during the breeding season, I found tyrosinase to be present, although the coloration was slow to develop (72 hrs.). It is possible that all of the tyrosinase in the ovary was used up in the production of the egg pigment, and that the oxidase for the tadpole is introduced by the male. It is well known that oxidative processes proceed much more rapidly after fertilization and perhaps we may find that in other instances this is due to the entrance of an oxidase with the sperm. Evidences of oxidase action have been found in all of the fertilized amphibian eggs that I have examined, including eggs which contain no pigment.¹ It is also possible that the "poisonous complex," to which Loeb (*Arch. Entw. Organ.*, 31, p. 658) ascribes the death of the unfertilized egg, is destroyed by the entrance of an oxidase (perhaps a *specific* oxidase) with the sperm.

85 (694)

On two different types of melanin.

By ROSS AIKEN GORTNER.

[*From the Laboratory of Biological Chemistry of the Station for Experimental Evolution, The Carnegie Institution of Washington.*]

In investigating the nature of the melanin molecule, I have found that the pigment which is present in black wool is readily soluble in dilute sodium hydroxide, and that it is apparently a protein. To pigments of this nature I have given the name of melano-protein to distinguish them from both the unpigmented proteins and those other melanins, the nature of whose molecule is as yet unknown. The melano-protein which I have obtained from black wool contains no ash, showing that ash is not a part of this pigment, and also proving that this melanin does not contain iron. In some of the preparations of pigment from black wool where less precautions were taken to insure the absence of all contaminating mineral matter, a low percentage of ash was ob-

¹ In collaboration with Dr. Banta, of this station, I have recently had occasion to test fertilized eggs of *Rana sylvatica*, *Rana pipiens*, *Ambystoma punctatum*, and *Spelerpes bilineatus*.

tained (0.10 per cent.—0.20 per cent.) but this ash appeared as white particles and was probably silica.

When I undertook to prepare a melanin from black rabbit hair and black feathers I found that the pigment was very *insoluble* in dilute (0.2 per cent.) sodium hydrate, and it was only after long boiling, in some instances nearly a week, that solution was effected. Of course this procedure altered the nature of the melanin molecule, but the fact that was of chief interest was that the resulting product contained between 2 per cent. and 3 per cent. of ash *and that this ash was chiefly iron oxide*. I have recently observed that there are probably at least two pigments in the darker colors of horse hair, one of these being a melano-protein with a very low ash content, and the other containing approximately 3 per cent. of ash *which is chiefly iron oxide*.

These pigments have been prepared in such a manner as to preclude any iron entering through contamination, and inasmuch as other pigments, *prepared by exactly the same process*, contain no iron, or at most only traces, we must conclude that *in some instances melanins may contain iron as a part of the molecule*, but that all melanins do not contain iron. Perhaps in this instance the oxidase acted on the hemoglobin, or some other iron complex, instead of oxidizing a protein containing no iron.

86 (695)

A five-year pedigreed race of Paramæcium without conjugation.

By **LORANDE LOSS WOODRUFF.**

[*From the Sheffield Biological Laboratory, Yale University.*]

The unicellular organisms afford a natural means of approach to the problem of fertilization, and the study of data, from a long series of careful experimental studies on these forms by various investigators, has pointed to the conclusion that the most important function of conjugation in the life history of the Protozoa is a satisfying of an inherent periodic physiological need of living matter, resulting in a renewal of the vigor of the cell. This "dynamic" view of fertilization has gradually assumed a com-

manding position, though it is neither contradictory nor confirmatory of the view that fertilization, resulting in amphimixis, is concerned in some way with the phenomenon of variation, or that it may be a process which enables certain forms to withstand changed environmental conditions.

The present paper briefly outlines the results which have been obtained to date from an intensive study of a pedigreed race of *Paramæcium aurelia* with reference to the problem of protoplasmic senescence and the function of conjugation. I have previously published¹ the results obtained to September, 1910, and the reader is referred to earlier papers for further details of the culture and for a general discussion of the various phases of the work.

This culture was started on May 1, 1907, with a "wild" *Paramæcium aurelia* which was isolated from a laboratory aquarium. This individual was placed in about five drops of culture medium on a glass slide having a central ground concavity, and when the animal by division had formed four individuals, each of these was isolated on a separate slide to form the four lines, Ia, Ib, Ic, and Id, of this culture, *Paramæcium* I. The pedigreed culture has been maintained by a specimen isolated from each of these lines practically every day up to the present time, thus precluding the possibility of conjugation occurring and facilitating an accurate record of the number of generations attained. A culture medium consisting of infusions of hay and fresh grass was employed during the first nine months of the work, but thereafter infusions of nearly any materials which might be found in ponds, swamps, etc., have been used. The medium has invariably been boiled to render the introduction of "wild" individuals into the culture absolutely impossible.

This race of *Paramæcium* has attained so far, (May 1, 1912) 3,029 generations during the five years it has been under daily observation. The number of generations attained during each of the first five years of its existence is as follows: first year 452, second year 690, third year 613, fourth year 612, and fifth year 662. The mean rate of division for the entire period is over three divisions in forty-eight hours. Periods of marked physiological depression have not occurred—such variations in the rate of

¹ *Archiv für Protistenkunde*, Bd. 21, 4.

reproduction as have appeared being either normal rhythms or the effects of environmental changes of temperature and culture medium. The organisms of the present generation are in as normal morphological and physiological condition as the original "wild" individual isolated to initiate the culture.

This study has demonstrated that, under favorable environmental conditions, the protoplasm of the cell originally isolated possessed (at least) the potentiality to produce similar cells to the number represented by 2 raised to the 3,029th power, or a volume of protoplasm approximately equal to 10^{1000} times the volume of the Earth. I believe this result proves beyond question that the protoplasm of a single cell may be self-sufficient to reproduce itself indefinitely, under favorable environmental conditions, without recourse to conjugation and clearly indicates that senescence and the need of fertilization are not primary attributes of living matter.

87 (696)

The influence of tartrates upon phlorhizin diabetes.

By **FRANK P. UNDERHILL.**

[From the Sheffield Laboratory of Physiological Chemistry, Yale University, New Haven, Conn.]

A recent communication of Baer and Blum (*Archiv für Experimentelle Pathologie und Pharmakologie*, 1911, 65, p. 1) shows that the subcutaneous administration of a number of organic compounds, containing two carboxyl groups, exercises a remarkable inhibitory influence upon the elimination of urinary nitrogen and dextrose in dogs with phlorhizin diabetes. Among the substances possessing this property may be mentioned glutaric and tartaric acids.

In an endeavor to explain the mechanism of the unique influence exerted by these compounds investigations have been carried out with tartrates upon both dogs and rabbits under conditions similar to those established by Baer and Blum. We have been able to corroborate the findings of Baer and Blum with respect to the action of tartrates although Ringer (*Proc. Soc. Exp. Biol.*

AND MED., 1912, 9, p. 54) failed to obtain the reported results with glutaric acid.

Our interpretation of the diminution of the urinary constituents is, however, entirely different from that offered by Baer and Blum. Tartrates subcutaneously injected cause a prompt disintegration of the cellular elements of the kidney tubules, leading to partial or complete loss of secretory activity, and in many cases to anuria. Hence, in phlorhizin diabetes urinary nitrogen and sugar are not eliminated to an appreciable extent.

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EXECUTIVE PROCEEDINGS.

Forty fifth meeting.

Columbia University, October 18, 1911. President Morgan in the chair.

Members present: H. M. Adler, I. Adler, Alsberg, Auer, Bancroft, Calkins, Field, Jackson, Joseph, Levene, Levin, Meltzer, Morgan, Pappenheimer, Senior, Simpson, Stewart, Wallace, H. B. Williams.

Forty sixth meeting.

The Rockefeller Institute for Medical Research, December 20, 1911. President Morgan in the chair.

Members present: Atkinson, Auer, Cohn, Davenport, Emerson, Eisenbrey, Field, Foster, Famulener, Fitzpatrick, Gies, Goldfarb, Hess, Jacobs, Janeway, Joseph, Lambert, Lee, Levin, Loeb, MacCallum, Manwaring, Meltzer, Morgan, Mosenthal, Norris, Ottenberg, Pappenheimer, Rous, Steinhardt, Swift, Terry, Wallace, Weil.

Members elected: A. M. Banta, E. C. Dickson, E. M. Ewing, J. G. Fitzgerald, R. A. Gortner, A. E. Guenther, W. de B. MacNider, B. S. Oppenheimer, F. H. Pike.

Forty seventh meeting.

College of the City of New York, February 21, 1912. President Morgan in the chair.

Members present: Alsberg, Atkinson, Bancroft, Fitzpatrick, Githens, Goldfarb, Guenther, Janeway, Joseph, Karsner, Kast, Kleiner, Lambert, Lee, Longcope, Lusk, Mandel, Meltzer, Morgan, McCrudden, Parker, Pike, Ringer, Senior, Stewart, Storey, Terry, Wallace, Winslow.

Members elected: E. E. Butterfield, A. F. Coca, George Draper, G. Canby Robinson, H. Wastenays, C. J. Wiggers.

Officers elected: President, James Ewing; Vice-president, P. A. Levene; Treasurer, Charles Norris; Secretary, George B. Wallace.

Resolution adopted: Resolved, that groups of members be allowed by special vote of the society to form local branches of the society: that such local branches be designated by local names, e. g., "The San Francisco Branch of the Society for Experimental Biology and Medicine;" and have power to hold meetings independently of the meetings of the society as a whole; that the expenses of such local meetings be borne by the local branches; that the members of such local branches have power to arrange their own programs and to publish their scientific papers in the proceedings of the society; and that only members of the society as a whole and who shall have been duly proposed to the council and elected in the manner provided for by the constitution be members of the local branches.

Forty eighth meeting.

Cornell University Medical College, April 17, 1912. President Ewing in the chair.

Members present: Auer, Bancroft, Benedict, Butterfield, Cohn, Ewing, Field, Fitzpatrick, Foster, Githens, Guenther, Hatcher, Kleiner, Lee, Levine, Longscope, Lusk, Manwaring, McCrudden, Meltzer, Mendel, Morgan, Murlin, Norris, Pappenheimer, Robinson, Steinhardt, Stewart, Stockard, Swift, Terry, Van Slyke, Wallace, Wiggers, H. B. Williams.

Members elected: J. H. Austin, H. E. Jordan, C. C. Lieb, F. W. Schlutz.

Resignation accepted: V. C. Vaughan.

Resolution adopted: Resolved, that abstracts of communications to be published in the Proceedings of the meeting at which they are presented must be delivered to the secretary not later than two days after the meeting; Otherwise they shall be published in the Proceedings of a subsequent meeting.

Forty ninth meeting.

University and Bellevue Hospital Medical College, May 15, 1912. President Ewing in the chair.

Members present: Auer, Bancroft, Banzhaf, Benedict, Birchard,

Butterfield, Calkins, Coca, J. W. Draper, Emerson, James Ewing, E. M. Ewing, Githens, Goldfarb, Harris, Hatcher, Jackson, Kleiner, Lambert, Lieb, J. A. Mandel, McCrudden, Murlin, Norris, Pike, Rous, Terry, Wallace, Weil, Wiggers, H. B. Williams, Winslow.

Members elected: M. T. Burrows, E. F. DuBois.

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Barnard Skin and Cancer Hospital (St. Louis).—Leo Loeb.

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Dates of the next two regular meetings:

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Dates of the next two regular meetings:

December 13, 1911 — February 21, 1912.

PROCEEDINGS
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EXPERIMENTAL BIOLOGY AND MEDICINE

FORTY-SEVENTH MEETING
COLLEGE OF THE CITY OF NEW YORK

NEW YORK CITY

FEBRUARY 21, 1912

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No. 3

NEW YORK

1912

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EXPERIMENTAL BIOLOGY AND MEDICINE

FORTY-EIGHTH MEETING

CORNELL UNIVERSITY MEDICAL COLLEGE

NEW YORK CITY

April 17, 1912

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PROCEEDINGS
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SOCIETY FOR
EXPERIMENTAL BIOLOGY AND MEDICINE

FORTY-NINTH MEETING

UNIVERSITY AND BELLEVUE HOSPITAL
MEDICAL COLLEGE

NEW YORK CITY

MAY 15, 1912

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No. 5

NEW YORK

1912

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University College (London).—Arthur R. Cushny.

Phipps Institute (Philadelphia).—Paul A. Lewis.

Wistar Institute of Anatomy (Philadelphia).—H. H. Donaldson, Shin-kishi Hatai, E. B. Meigs.

Barnard Skin and Cancer Hospital (St. Louis).—Leo Loeb.

Members present at the forty-eighth meeting:

Auer, Bancroft, Benedict, Butterfield, Cohn, Ewing, Field, Fitzpatrick, Foster, Githens, Guenther, Hatcher, Kleiner, Lee, Levine, Longcope, Lusk, Manwaring, McCrudden, Meltzer, Mendel, Morgan, Murlin, Norris, Pappenheimer, Robinson, Steinhardt, Stewart, Stockard, Swift, Terry, van Slyke, Wallace, Wiggers, Williams.

Members elected at the forty-eighth meeting:

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Dates of the next two regular meetings:

May 15, 1912—October 16, 1912.

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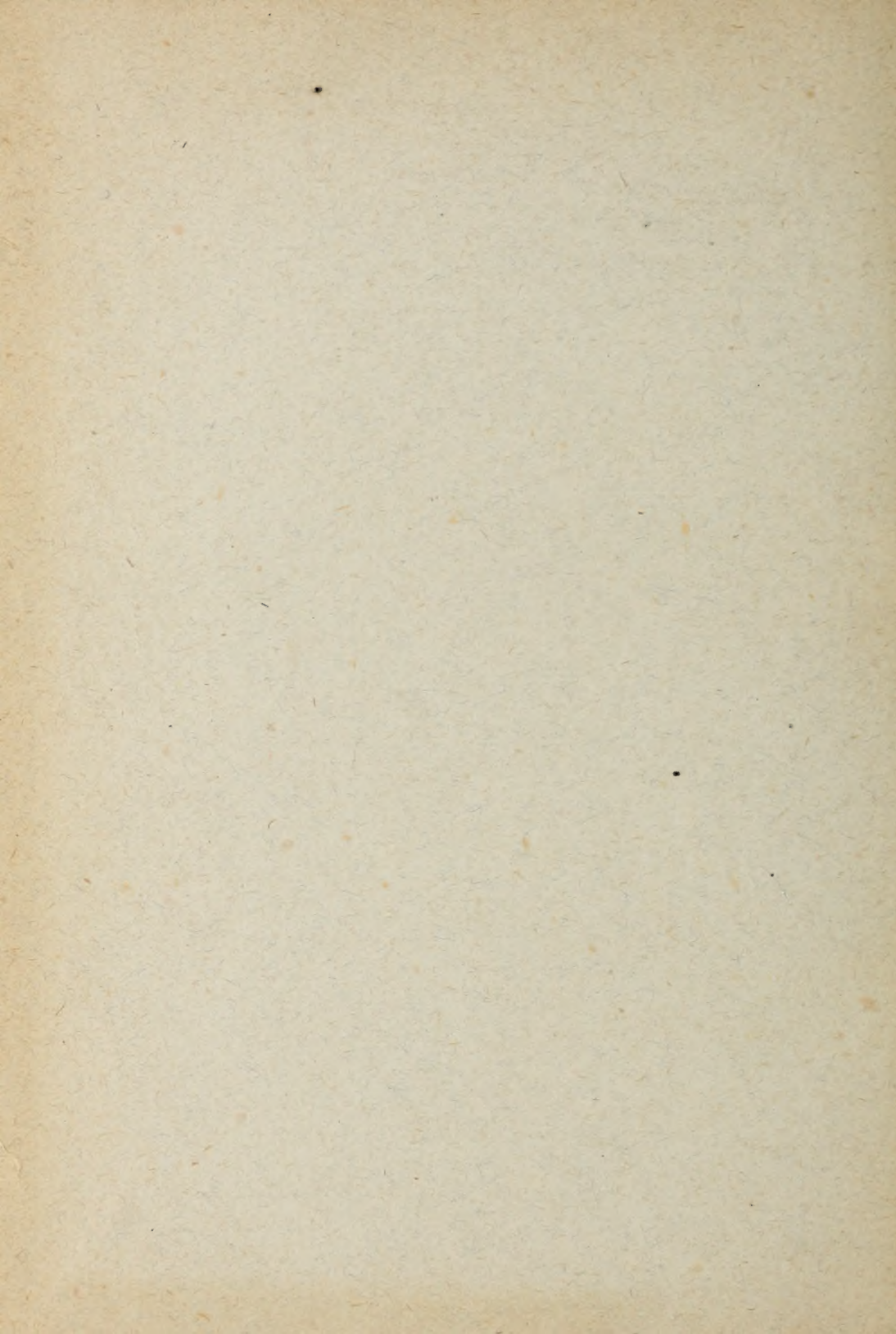
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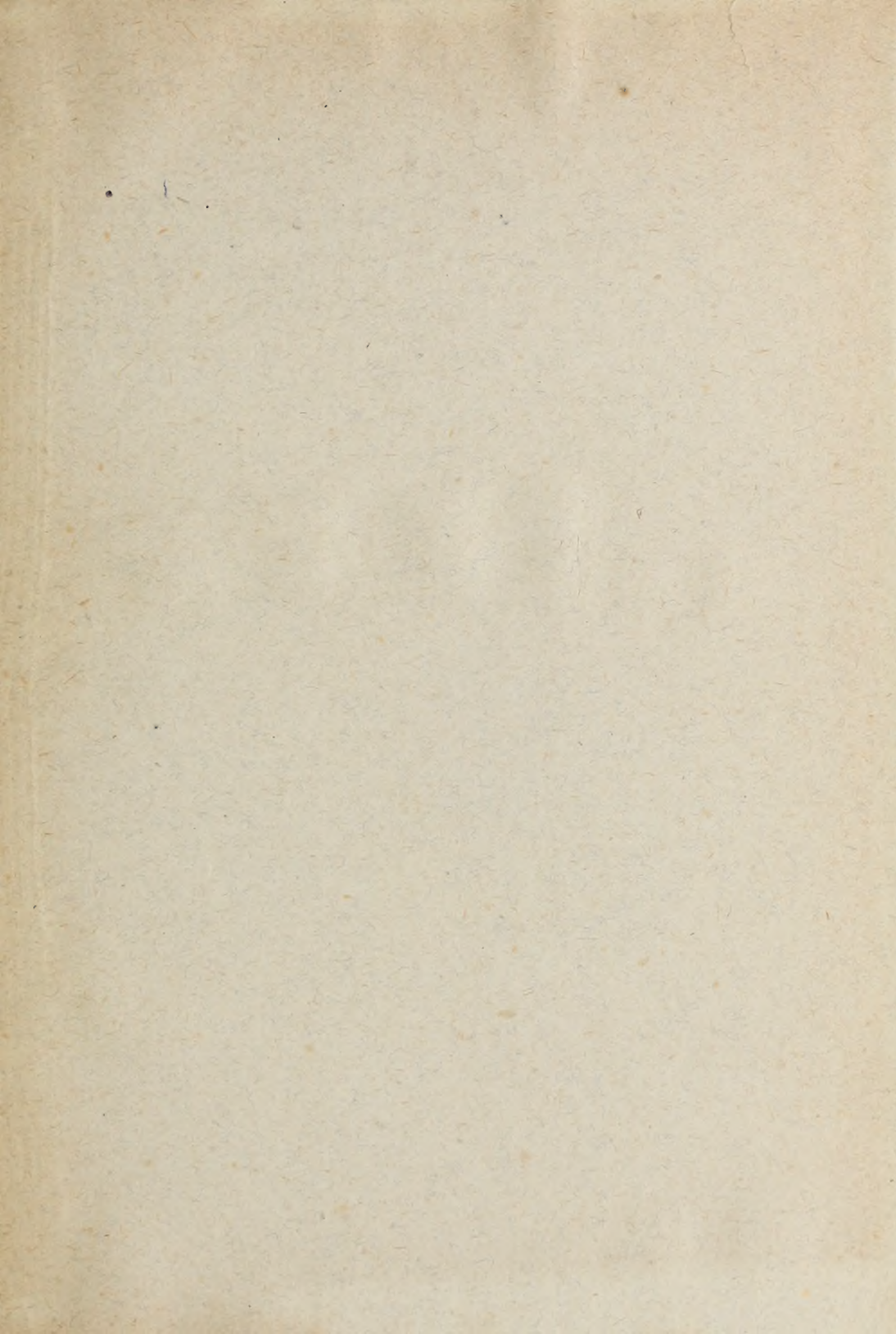
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Dates of the next two regular meetings:

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